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December, 1960
volume 80, number 6
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Vol. 80, No. 6, December, 1960. American Journal of Obstetrics and Gynecology is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: United States and its Possessions $15.00; Canada, Latin America, and Spain $16.00; Other Countries $17.50. Special rate for medical students and physicians on internship or residency programs, one half of the domestic rate; for students in other countries, one half of the domestic rate plus the full amount of the applicable charge for international postage. Single copies $2.50 postpaid. Second-class postage paid at St. Louis, Mo.
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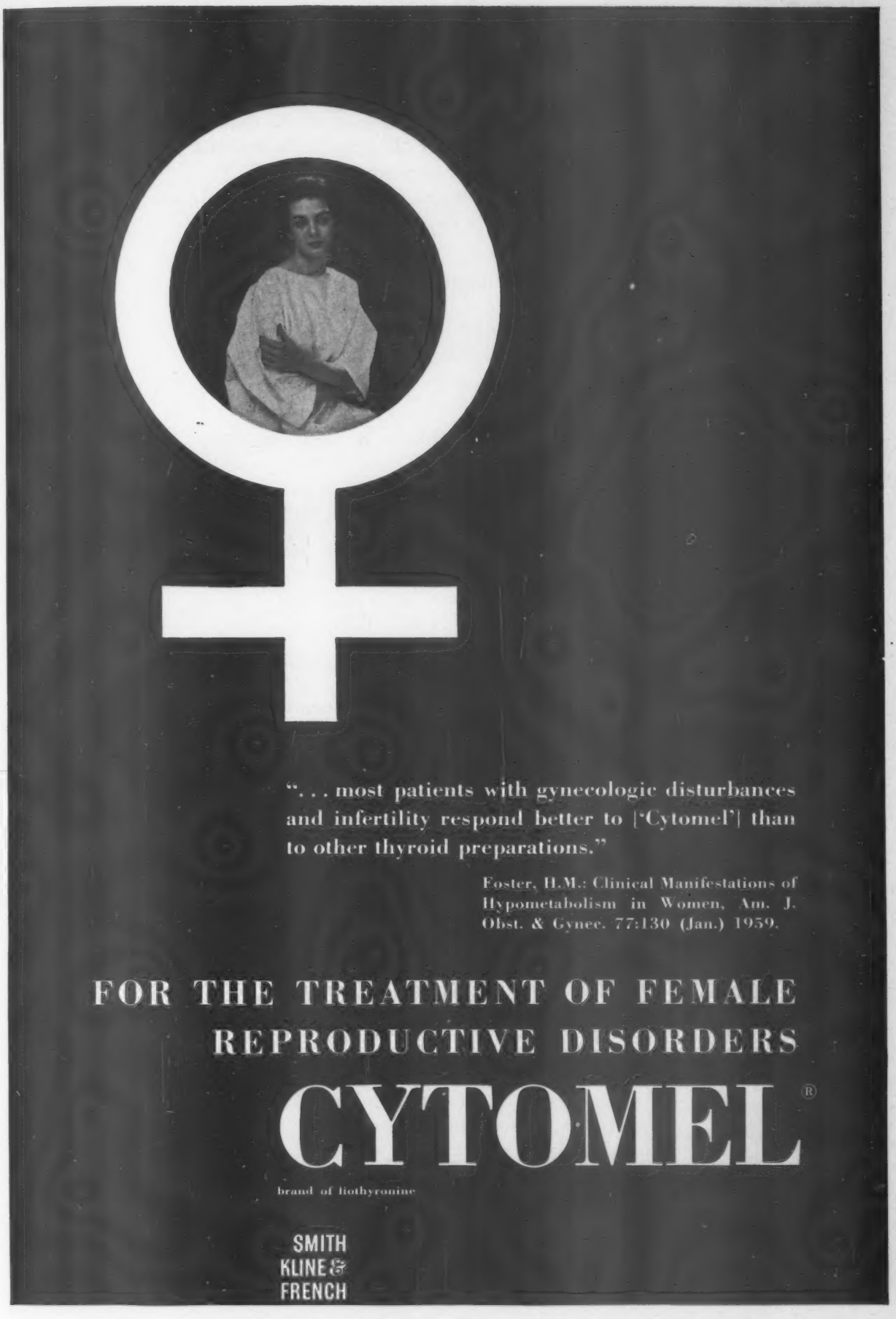
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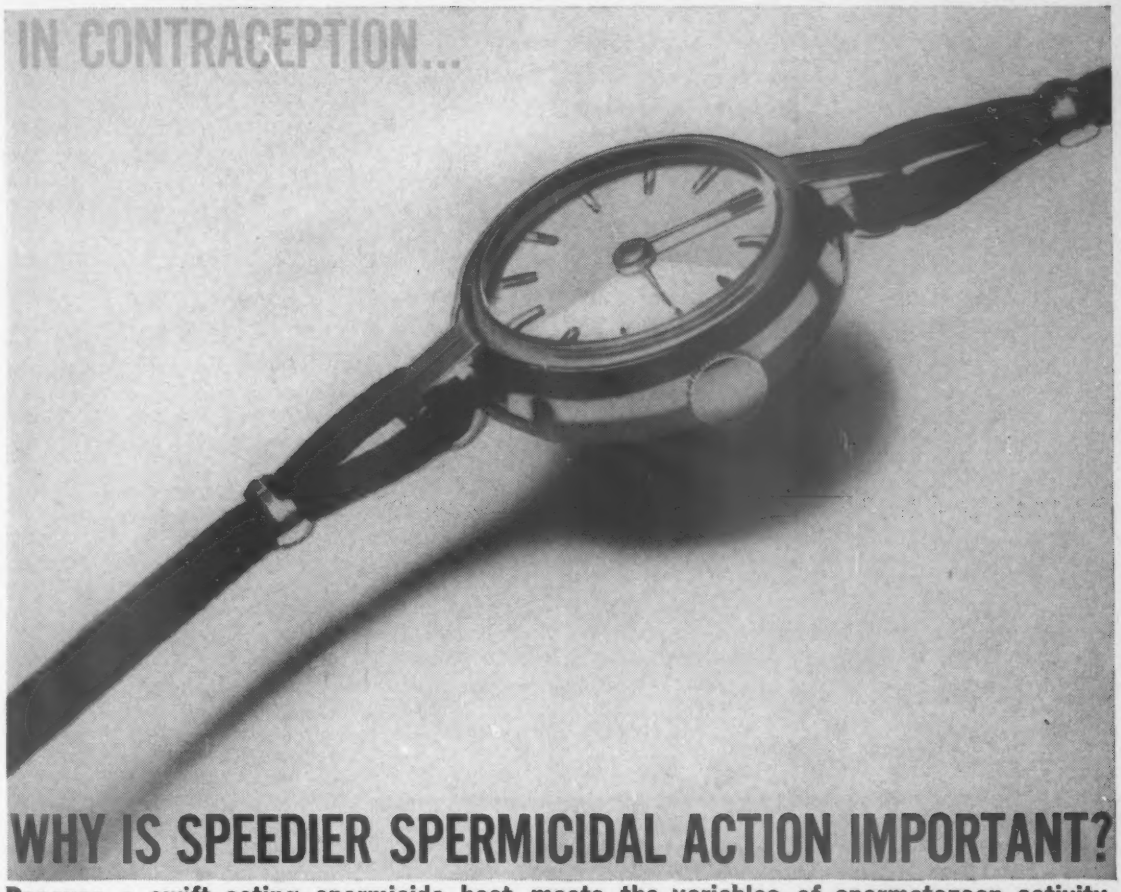

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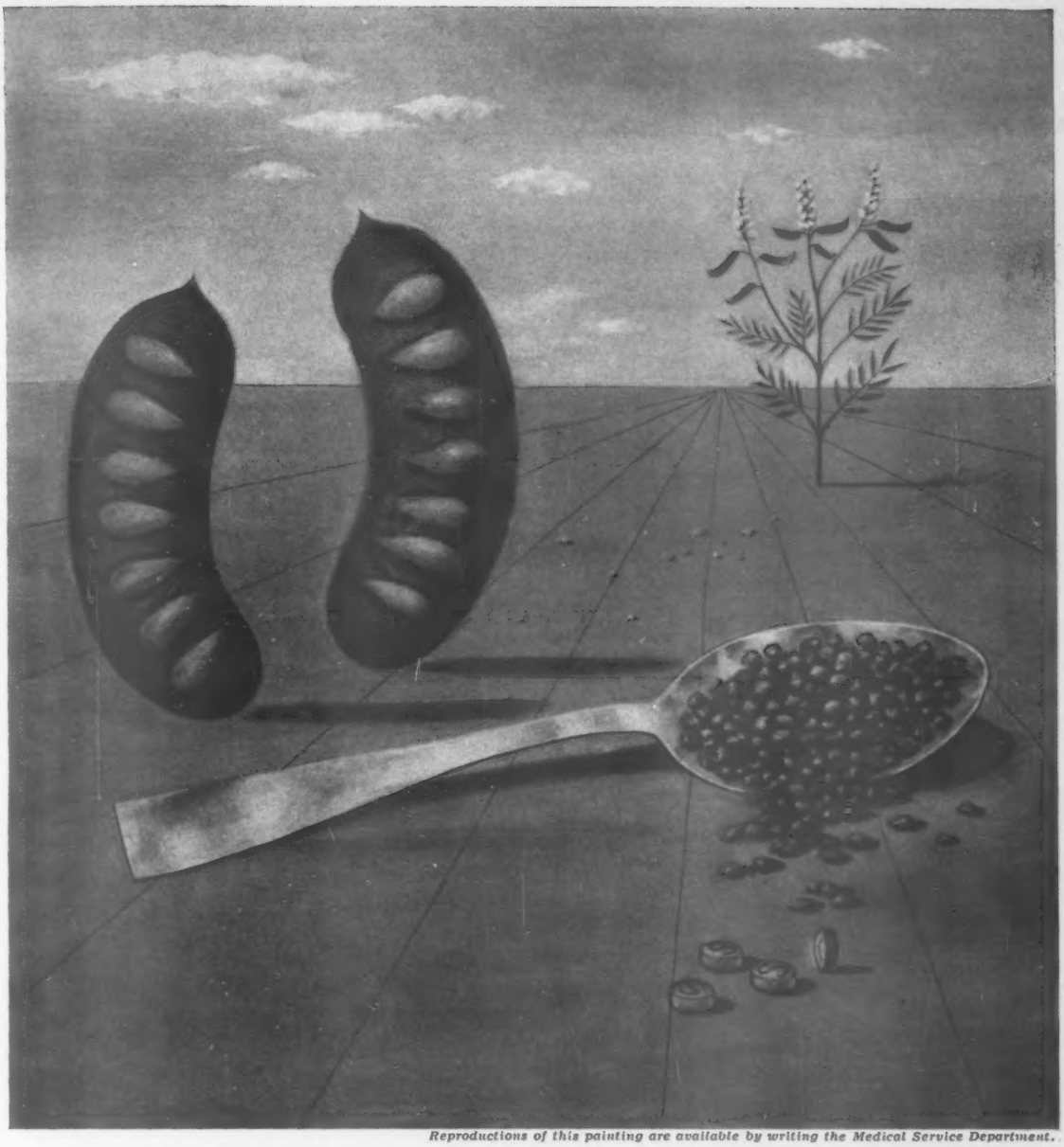

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Publisher

The C. V. Mosby Company
3207 Washington Blvd., St. Louis 3, Missouri

Entered at the Post Office at St. Louis, Mo., as Second-Class Matter

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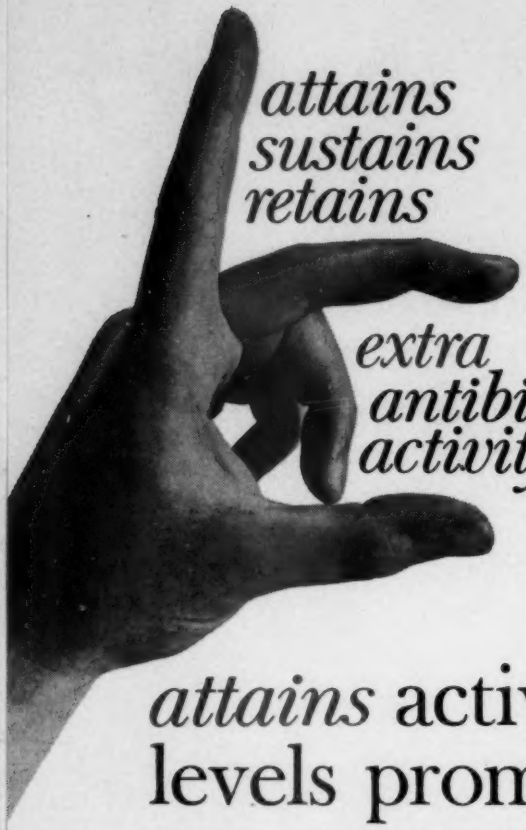

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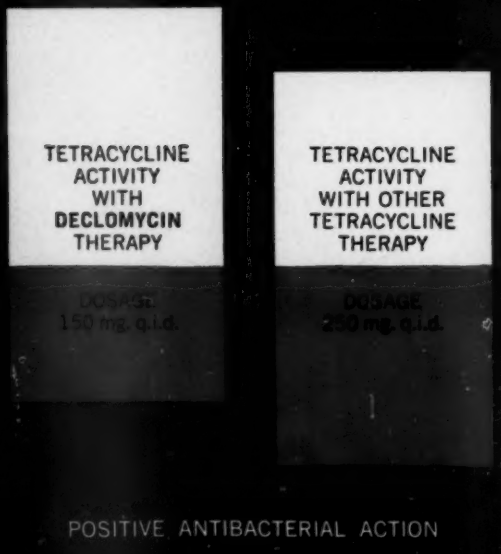
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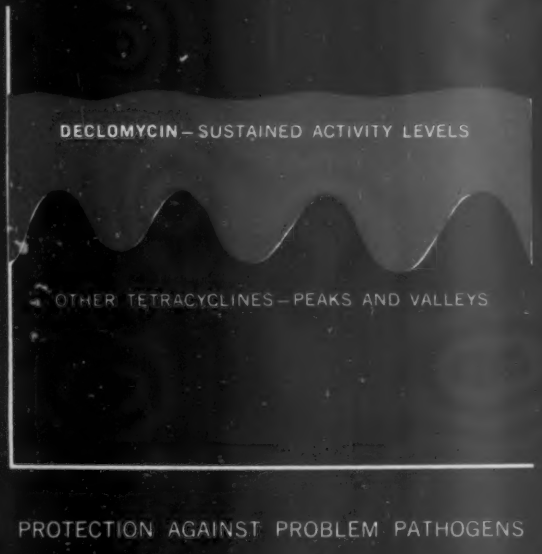

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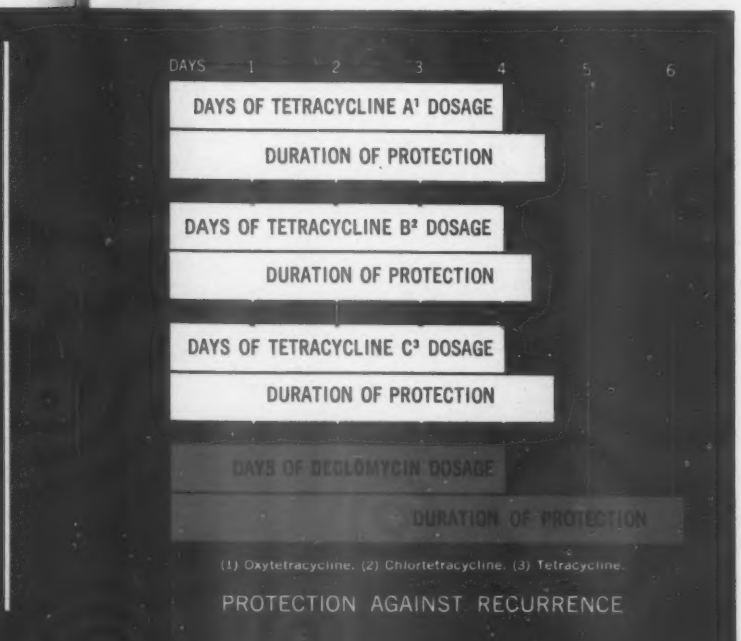
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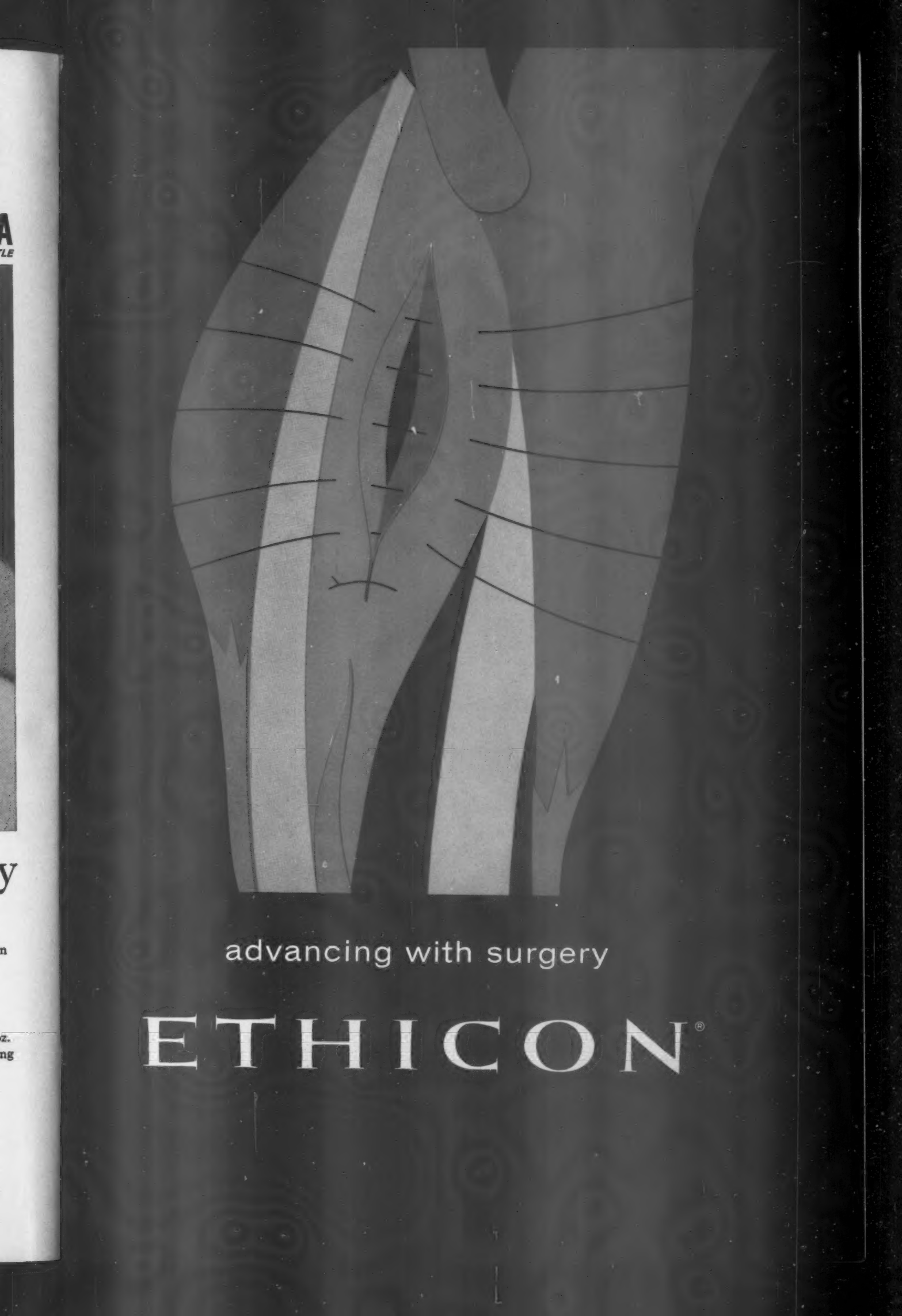
1. Rosenfield, H. H., et al.: Obst. & Gynec. 11:222, 1958. 2. Bookmiller, M. M., and Bowen, G. L.: Textbook of Obstetrics and Obstetric Nursing, ed. 3, Philadelphia, Saunders, 1958, p. 314. 3. Heilman, L. D.: Gastroenterology.

C. B. FLEET CO., INC. Lynchburg, Virginia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You can see for yourself the efficient detergent action of Trichotine solution in reducing promptly a cervical plug (using a saturated cotton pledget), or washing away the "cheesy" exudate of monilia.

TRICHOTINE is just as effective for therapeutic irrigation by your patient at home

The same qualities – detergency,* antisepsis, healing – make Trichotine ideal for the treatment of cervico-vaginitis and leukorrheas, alone or in conjunction with other antimicrobials. In the itching, burning, and foul odor of non-specific vaginitis and leukorrhea the action of Trichotine is immediate and gratifying to the patient.

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The modern detergent douche

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RADIOPAQUE PENROSE DRAINS
BY DAVOL

TWO major improvements that provide a greater sense of security for patient, hospital and physician:

1. **CENTIMETER CALIBRATION:** Permits rapid, accurate evaluation of the length of the indwelling portion of the Penrose Drain.
2. **RADIOPACITY:** Flat-plate radiographic examination discloses presence—or absence—of drain within a body cavity. Makes X-ray examination a simple method for determining retention of the drain within a cavity.

Research and development of the new radiopaque centimeter-calibrated Penrose Drains have been conducted in collaboration with: Dr. Donald F. McDonald, Chief of Urology, Strong Memorial Hospital; Professor of Urology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Dr. Walter J. Pories, Department of Surgery, Strong Memorial Hospital, Rochester, N. Y. Dr. Leonard H. Flax, Washington Hospital Center, Washington, D. C.

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Each of the babies pictured on this page was borne by a mother with a *documented* previous history of true habitual abortion, who was treated with DELALUTIN during the pregnancy leading to this birth

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DELALUTIN

SQUIBB HYDROXYPROGESTERONE CAPROATE

Improved Progestational Therapy

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DELALUTIN offers these advantages over other progestational agents

• long-acting sustained therapy • more effective in producing and maintaining a completely matured secretory endometrium • no androgenic effect • more concentrated solution requiring injection of less vehicle • unusually well-tolerated, even in large doses • fewer injections required • low viscosity makes administration easy

Complete information on administration and dosage is supplied in the package insert

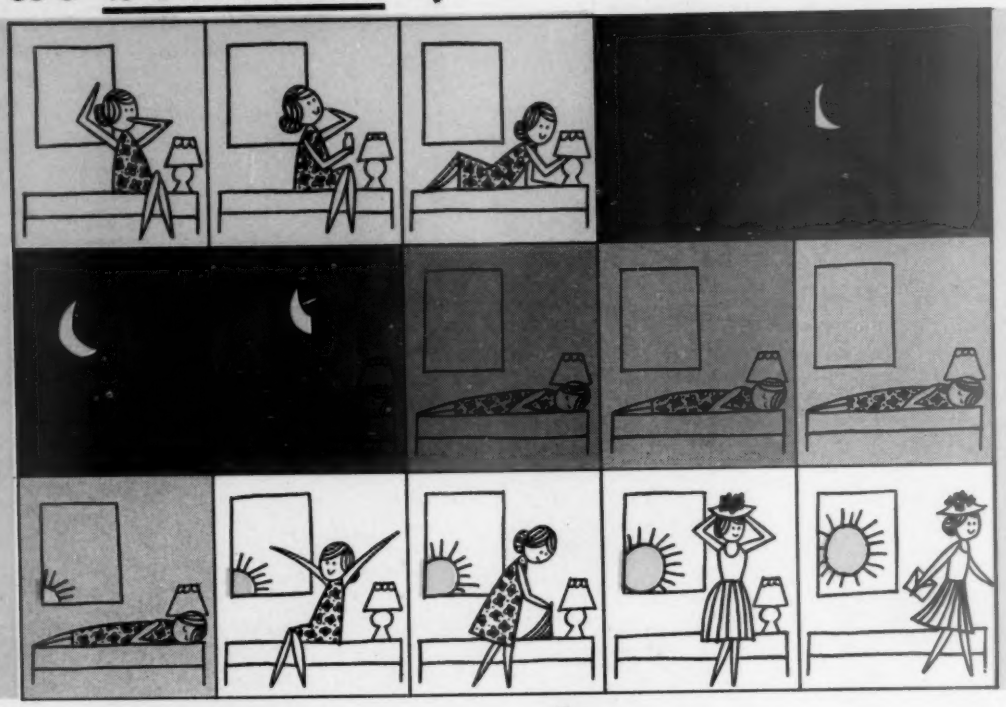
Supply: Vials of 2 and 10 cc., each containing 125 mg. of hydroxyprogesterone caproate in benzyl benzoate and sesame oil.

SQUIBB *Squibb Quality—The Priceless Ingredient*

'DELALUTIN'® IS A SQUIBB TRADEMARK

BENDECTIN

at bedtime ↘



prevents
morning sickness
here!

"... I have gained the best results with [Bendectin]... Because these tablets have a protective coating... the dose taken at night becomes effective in the morning."[1]

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS[2]

Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTAL 94%		
Placebo	57	13 (23%)	24 (42%)	20 (35%)
		TOTAL 65%		

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."[2]

Measure Bendectin against your present Rx:

Q. Has your present Rx been shown to relieve morning sickness — before it starts — in more than 9 out of 10 patients?[2-5]

Q. Is your present Rx free of phenothiazine-like side effects and habituating properties?

Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

With Bendectin, the answer to all three is YES.

FORMULA:
Each white, specially coated tablet contains:
Bentyl (dicyclomine) hydrochloride ..... 10 mg.
Decapryn (doxylamine) succinate ..... 10 mg.
Pyridoxine hydrochloride ..... 10 mg.

DOSAGE: Two tablets at bedtime.

SUPPLY: Bottles of 100 and 500.

1. Middleton, T. F.: Postgrad. Med. *24*:699, 1958.
2. Geiger, C. J., *et al.*: Obst. & Gynec. *5*:688, 1959.
3. Nulsen, R. O.: Ohio State M. J. *53*:665, 1957.
4. Personal communications, 1956-57.
5. Towne, J. E.: Internat. Rec. Med. *171*:583, 1958.

TRADEMARKS: BENDECTIN®, BENTYL®, DECAPRYN®

Merrell **The Wm. S. Merrell Company**
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NaClex®

benzthiazide

a new diuretic with an unsurpassed faculty for salt excretion

as salt goes, so goes edema

A basic principle of diuresis is that "increased urine volume and loss of body weight are proportional to and the osmotic consequences of loss of ions."[1]

Robins' new NaClex is a potent, oral, non-mercurial diuretic that helps reduce edema through the application of this fundamental principle. It limits the reabsorption of sodium and chloride in the renal proximal tubules (*with a relative sparing of potassium*). The body's homeostatic mechanism responds by increasing the excretion of excess extracellular water. Thus the NaClex-induced removal of salt leads to a reduction of edema.

a unique chemical structure

NaClex (benzthiazide) is a new molecule which provides a "pronounced increase in diuretic potency"[2] over its antecedent sulfonamide compound. Compared tablet for tablet with current oral diuretics, it is unsurpassed in diuretic potency.

twofold value

NaClex produces diuresis, weight loss, and symptomatic improvement in edema associated with various conditions. It also has antihypertensive properties and may be used alone in mild hypertension or with other antihypertensive drugs in severer cases.

For complete dosage schedules, precautions, or other information about NaClex, please consult basic literature, package insert, or your local Robins representative, or write to the A. H. Robins Co., Inc.

Supply: Yellow, scored 50 mg. tablets.

References: 1. Pitts, R. F., Am. J. Med., 24:745, 1958. 2. Ford, R. V., Cur. Therap. Res., 2:51, 1960.

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RICHMOND 20, VIRGINIA

Helps you take the misery out of menopause

as hormones alone often don't do

Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).
Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.
Literature and samples on request.

Milprem®

(Miltown® plus natural estrogens)

DMF-1206

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

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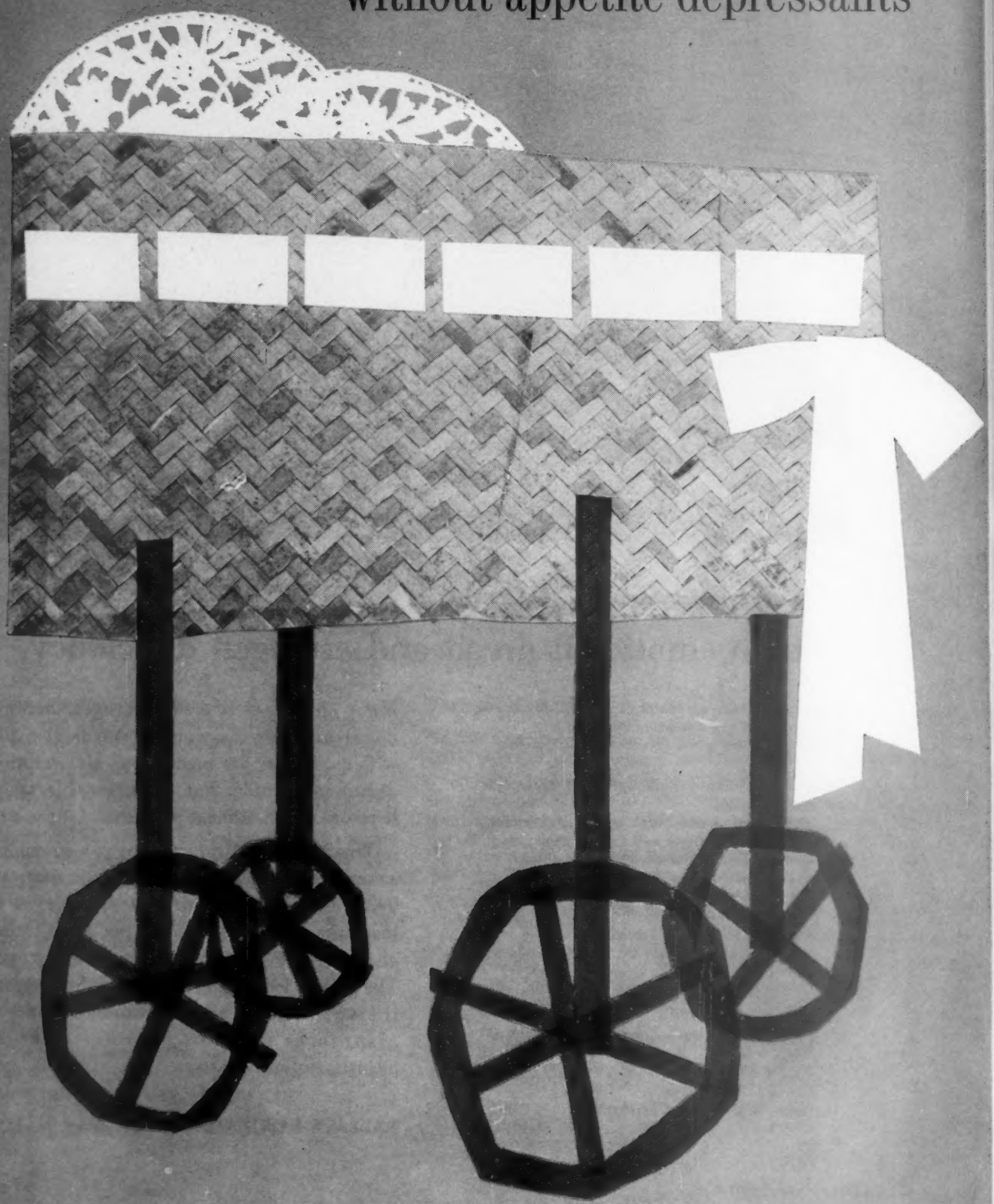
measured calories with high satiety

...to help control your pregnant patient's weight

without appetite depressants



METRECAL™

DIETARY FOR WEIGHT CONTROL

sound nutrition with limited calories

Metrecal may be used as the cornerstone of a pregnancy diet to avoid too-rapid weight gains or to effect desirable reduction. The 900-calorie daily ration provides 70 Gm. of protein, plus all essential vitamins and minerals including generous amounts of calcium (2.0 Gm.) and iron (15 mg.).

highly flexible

When substantial weight loss is indicated, Metrecal *alone* can provide the complete diet. Metrecal can also be used for one or two meals a day or as the total diet two or three days a week. Postpartum, Metrecal provides an excellent method for losing weight or preventing additional weight gain.

patient cooperation shown clinically

The high satiety, simplicity of use, and palatability of Metrecal provide patients with a strong motivation to cooperate in weight-control programs.[1,2,3] Metrecal relies on sound nutritional principles for weight control. No appetite depressants or complex diets are required.

And now for maximum convenience!
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Individual 8 oz. 225 calorie pre-mixed servings. Each can provides a delicious, sustaining meal. Just open, pour and serve—supplied in Chocolate, Vanilla, and Butterscotch flavors. Also available in powder.

references

(1) Antos, R. J.: The Use of a New Dietary Product (Metrecal) For Weight Reduction, Southwestern Med. *40*:695-697 (Nov.) 1959. (2) Tullis, I. F.: Initial Experience with a Simple Weight Control Formula, to be published. (3) Roberts, H. J.: Effective Long-Term Weight Reduction—Experiences with Metrecal, to be published.

Mead Johnson
Symbol of service in medicine

09360

on the pathogenesis of pyelonephritis

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."[1]

Recent experimental evidence in animals strongly supports the view that obstruction of the tubules in the medulla, as opposed to the cortex, predisposes the kidney to pyelonephritis,[2] and ". . . as few as 10 organisms injected into the medulla were capable of causing infection."[3]

The "exquisite sensitivity"[4] of the medulla to infection highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."[5]

An agent, such as FURADANTIN, which has a specific affinity for the urinary tract and which is actively excreted by the cells of the tubules, as well as of the glomeruli,[6] is particularly suited to meet the problems posed by the pathogenesis of pyelonephritis and the primary pathways of infection.

in pyelonephritis
to eradicate the pathogens
no matter the pathway

FURADANTIN®

brand of nitrofurantoin

high urinary concentration
glomerular filtration
tubular excretion

effective at glomerular and tubular levels: In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

rapid antibacterial action: Antibacterial concentrations of FURADANTIN are in the urine in 30 minutes.

broad bactericidal spectrum: FURADANTIN is bactericidal against a wide range of gram-positive and gram-negative bacteria including certain organisms resistant to other agents.

free from resistance problems: Development of bacterial resistance to FURADANTIN has not been a problem in over 8 years of extensive clinical use.

well tolerated—even after prolonged use: FURADANTIN is nontoxic to kidneys, liver and blood-forming organs. No monilial superinfection, staphylococcic enteritis, proctitis or anovulvar pruritus has ever been reported.

no cross resistance or cross sensitization with other drugs: FURADANTIN, a synthetic nitrofuran, is unrelated chemically to any other class of antimicrobial drugs; cross resistance or cross sensitization does not occur.

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d. with meals and with food or milk on retiring. SUPPLIED: Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Schreiner, G. E., A.M.A. Arch. Int. M. **102**:32, 1958. 2. Rocha, H., et al.: Yale J. Biol. & Med. **32**:120, 1959. 3. Freedman, L. R.: Yale J. Biol. & Med. **32**:272, 1960. 4. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. **30**:406, 1958. 5. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958. 6. Paul, M. F., et al.: Am. J. Physiol. **197**:580, 1959.

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"Intravenous PITOCIN may be used successfully in elective or indicated inductions of labor. It has a definite place in the stimulation of labor in the early part or later stages either in desultory preliminary labor, or in primary or secondary uterine inertia."*

PITOCIN (oxytocin injection, Parke-Davis) is supplied in 0.5-cc. (5-unit) ampoules, in boxes of 10 and in 1-cc. (10-unit) ampoules, in boxes of 10. Each cc. contains 10 international oxytocic units (U.S.P. units).

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*Fields, H.; Greene, J. W., Jr., & Franklin, R. R.: *Obst. & Gynec.* 13:353, 1959.

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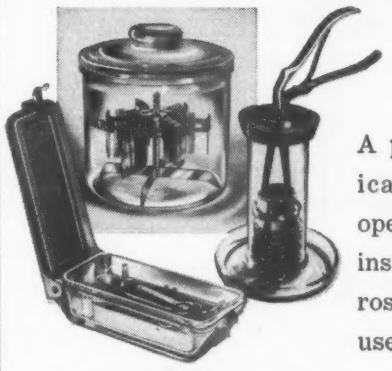

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In over five years

...for the tense and nervous patient

Despite the introduction in recent years of "new and different" tranquilizers, Miltown continues, quietly and steadfastly, to gain in acceptance. Meprobamate (Miltown) is prescribed by the medical profession more than any other tranquilizer in the world.

The reasons are not hard to find. Miltown is a ***known*** drug. Its few side effects have been fully reported. ***There are no surprises in store for either the patient or the physician.***

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Proven
in more than 750 published clinical studies

Effective
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Outstandingly Safe

1. simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
3. does not produce ataxia, change in appetite or libido
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meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

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ready for
immediate use to
soothe, protect,
stimulate
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WOUNDS
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(decubitus, diabetic, varicose)
lacerated, denuded,
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*complete report by bacteriologists on request.

For **samples** of Desitin Ointment write...

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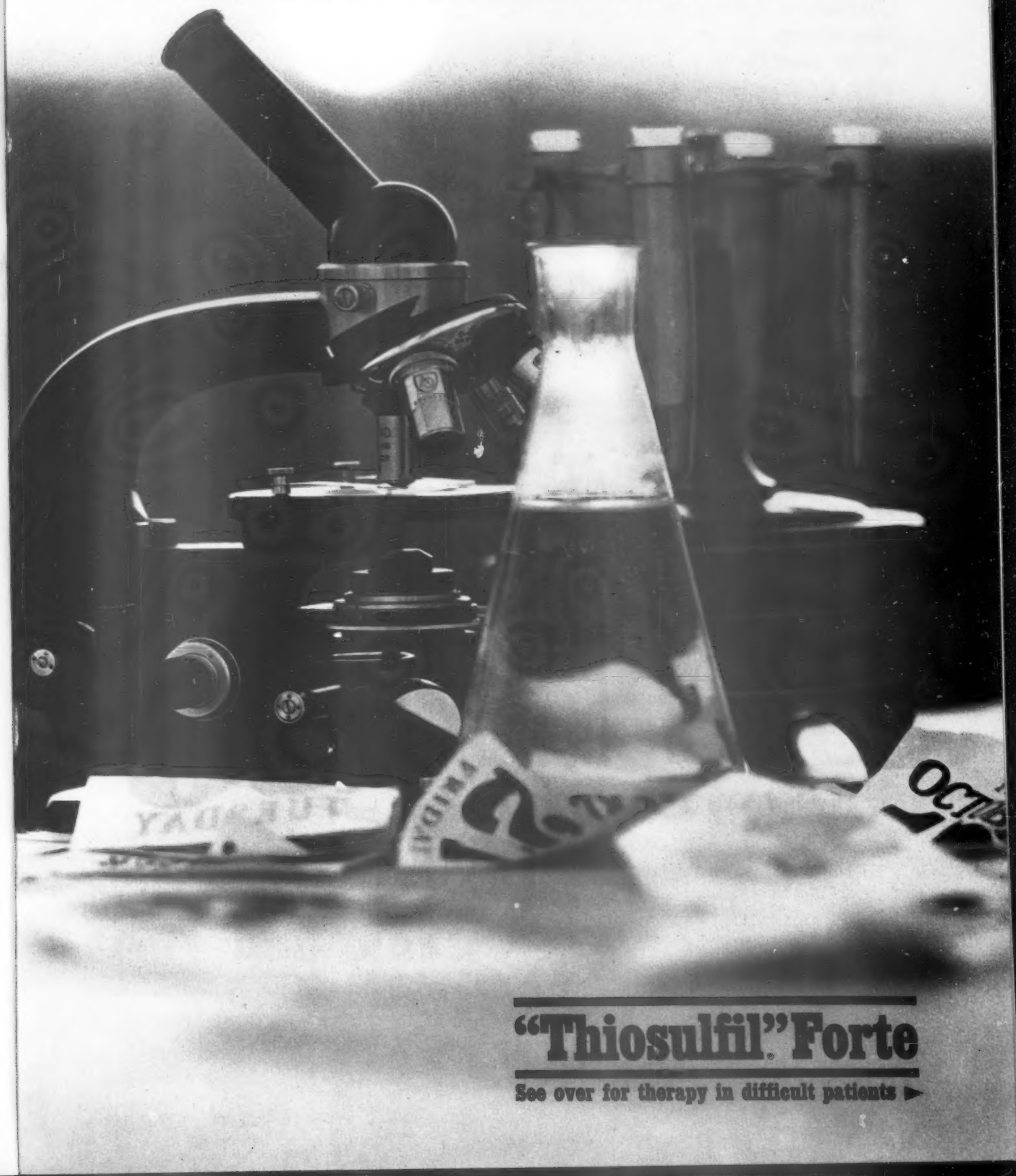
THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.



"Thiosulfil" Forte

See over for therapy in difficult patients ►

HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.

RECORD OF SAFETY

In clinical studies of over 3,600 patients, the number of reactions, none serious, was less than 2 per cent.[1-6] " 'Thiosulfil' was remarkably well tolerated, there being no discontinuation of treatment due to untoward effects, and very few mild reactions were noted."[2] "The drug can be taken over a long period of time with practically no untoward side reactions."[3] "Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not."[4] Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.[1] NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

PROOF OF EFFECTIVENESS

A review of more than 3,600 reported cases on "Thiosulfil" demonstrates: a) adequate drug dosage can be simply and economically achieved with a minimum incidence of complicating side effects; b) the antibacterial agent can be given over longer periods of time, particularly in cases involving urinary stasis.

Specific For Urinary Tract Infections: "Thiosulfil" reaches greater urinary concentrations in the active, free, nonmetabolized form than any other sulfa, single or mixed. "Thiosulfil" is rapidly excreted; as much as 79% of the drug is found in the urine after eight hours—of this, 98% is in the active form.[5] The entire g.u. tract is, thus, subjected to continual "sulfa baths" of active drug—more wide spectrum antibacterial activity at site of infection.

Even where urinary stasis exists and cannot be readily corrected, prolonged or even indefinite use of "Thiosulfil" on a reduced dosage schedule will usually keep the infection under control, patients comfortable, and side effects minimal. "Thiosulfil" may materially reduce the likelihood of infections ascending to the parenchyma of the kidneys and subsequent serious systemic involvement.

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day[1]
2 weeks to 3 months	2 Gm./day[2, 6]
3 months or longer	0.5 Gm./day[7]

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. Note: The usual precautions exercised with sulfonamides should be observed.

Supplied: No. 786: Each tablet contains 0.5 Gm. sulfamethizole; in bottles of 100 and 1,000 scored tablets.

References—1. Bourque, J-P., and Gauthier, G-E.: Seven years' experience with sulfamethizole, to be published. 2. Bourque, J-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953. 3. Barnes, R. W.: J. Urol. 71:655 (May) 1954. 4. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954. 5. Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, Apr. 6-9, 1959, San Francisco, California. 6. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:66 (Mar.) 1959. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.

"Thiosulfil"® Forte
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she wants the answer now!

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50 mg. anhydrohydroxyprogesterone, activated by 0.03 mg. ethinyl estradiol per tablet

permits quick, highly accurate early diagnosis

If the patient is not pregnant, and previously has had regular menstrual cycles, progesterone-withdrawal bleeding will occur within a few days after administration of the PRO-DUOSTERONE test (4 tablets a day for 3 days).

The PRO-DUOSTERONE test approaches 100% accuracy in normally-cycling women.[1]

If the patient is pregnant the progestational effect of PRO-DUOSTERONE actually serves to protect the pregnancy.

The PRO-DUOSTERONE test for pregnancy can be performed as early as a week after the missed menstrual period.

1. Schwartz, H.A.: Editorial, Minnesota Medicine 42:1279, September, 1959.

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EVERYONE IS RELIEVED WHEN URECHOLINE® Chloride (Bethanechol Chloride) REPLACES CATHETERIZATION

· *relief for the patient*

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URECHOLINE

HELPS CONTROL URINARY RETENTION—
PHYSIOLOGICALLY

· *relief for the physician*
—'Urecholine' eliminates the danger of infection which often follows instrumentation.

· *relief for the nurse*
— prophylactic and therapeutic use of 'Urecholine' makes available valuable nursing time for other purposes.

supplied: 5 mg. and 10 mg. tablets, bottles of 100. 1-cc. ampuls containing 5 mg.

for additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

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*Council on Drugs, J.A.M.A. 172:699, 1960.

Information on dosage, administration and precautions contained in official package circular, or available on request.

SUPPLY: KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in vial containing 2 ml. volume. KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in vial containing 3 ml. volume.

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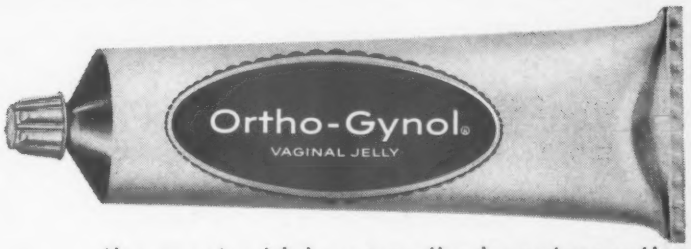
while she is planning
her family,

**she needs your help
more than ever**



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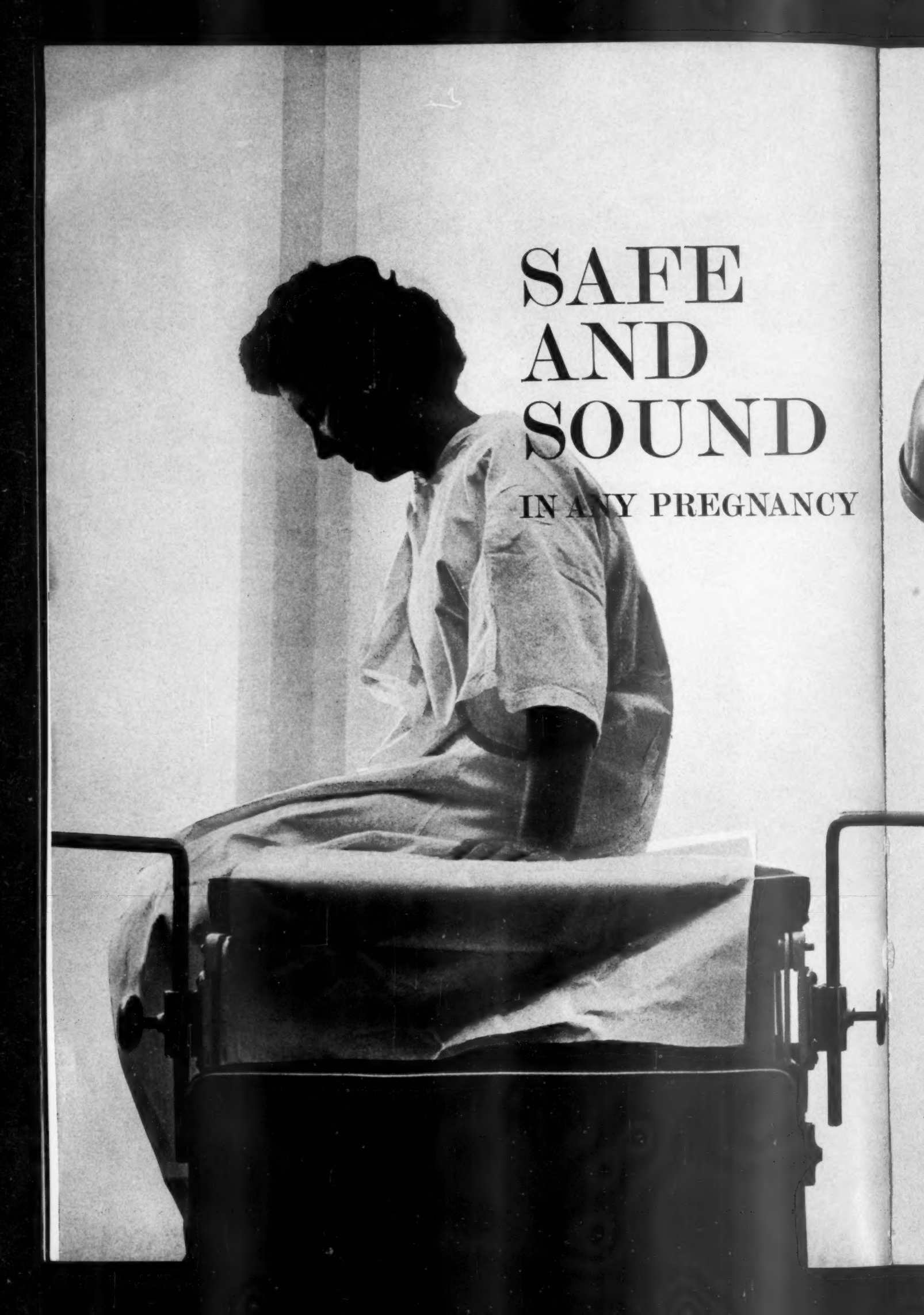
SAFE
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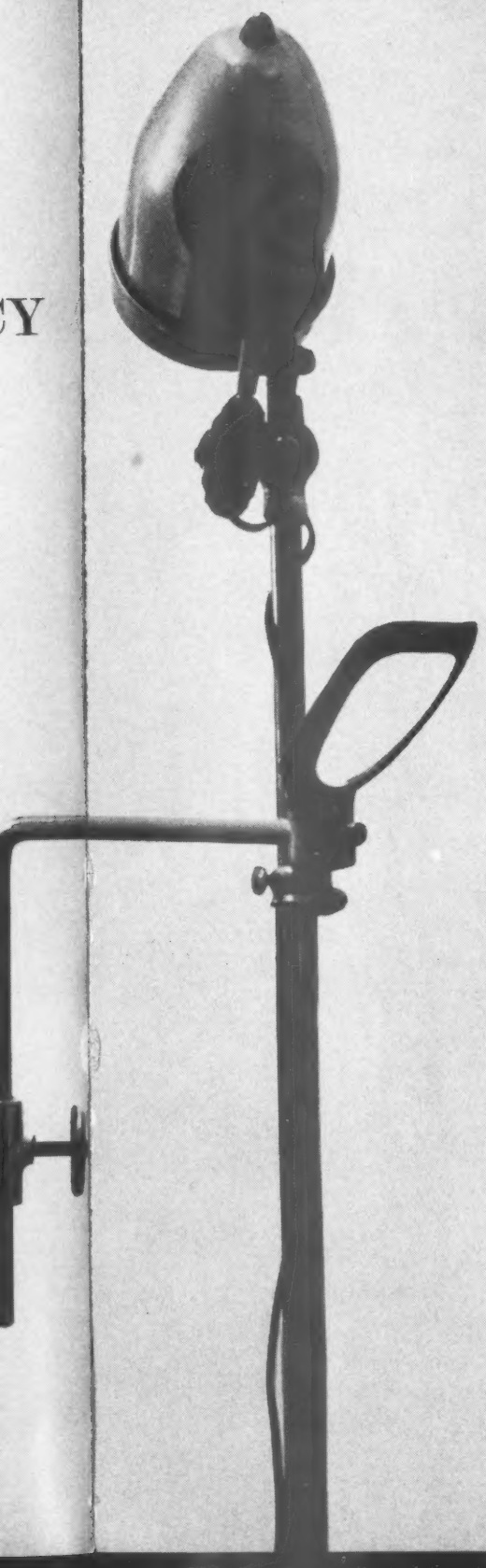
SOUND
IN ANY PREGNANCY

to prevent morning sickness



With new Tigan 250 mg capsules you can now provide protection against morning sickness with only two capsules daily — one at bedtime and one in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding the risks of phenothiazine derivatives and the limitations of the antihistamines, Tigan acts both therapeutically and prophylactically to stop active vomiting or to prevent nausea and vomiting.

Consult literature and dosage information, available on request, before prescribing.

TIGAN BIBLIOGRAPHY: **1.** M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **2.** O. C. Brandman, *ibid.* **3.** J. A. Lucinian and R. H. Bohn, *ibid.* **4.** D. W. Molander, *ibid.* **5.** B. I. Shnider and G. L. Gold, *ibid.* **6.** W. S. Derrick, *ibid.* **7.** B. Wolfson and F. F. Foldes, *ibid.* **8.** L. McLaughlin, *ibid.* **9.** W. K. Gauthier, Discussant, *ibid.* **10.** H. E. Davis, Discussant, *ibid.* **11.** I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp., 9*:189, 1958. **12.** W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap., 126*:270, 1959. **13.** W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, *New York J. Med., 59*:4217, 1959. **14.** O. W. Doyle, *Clin. Med., 7*:43, 1960. **15.** L. A. Nathan, *Curr. Therap. Res., 2*:6, 1960. **16.** Council on Drugs, New and Nonofficial Drugs, *J.A.M.A., 172*:1038, 1960. **17.** O. L. Davidson, *J. Tennessee M.A., 53*:140, 1960. **18.** O. Brandman, *Gastroenterology, 38*:777, 1960. **19.** B. A. Robin, *Maryland M. J.*, in press. **20.** A. L. Kolodny, *Am. J. M. Sc., 239*:682, 1960. **21.** F. Cacace, *Colorado GP, 2*:5, 1960. **22.** J. W. Bellville, I. D. J. Bross and W. S. Howland, *Clin. Pharmacol. & Therap.*, in press.

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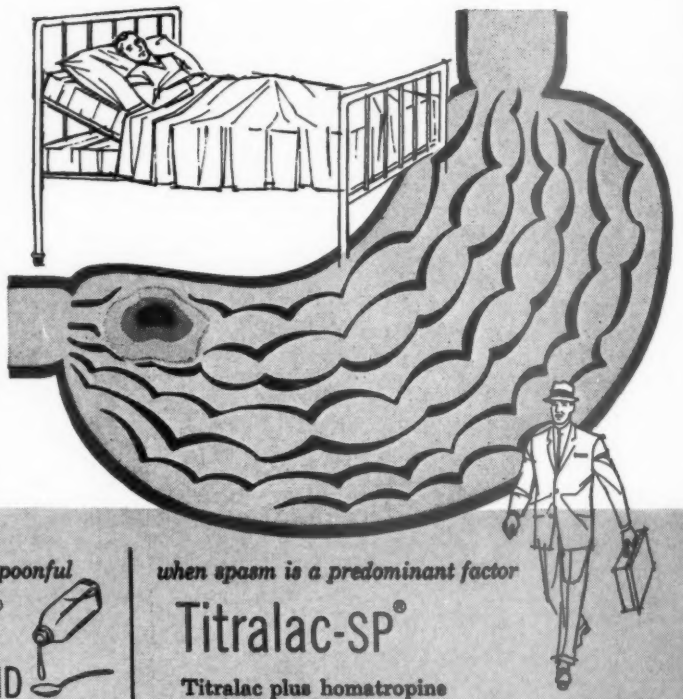

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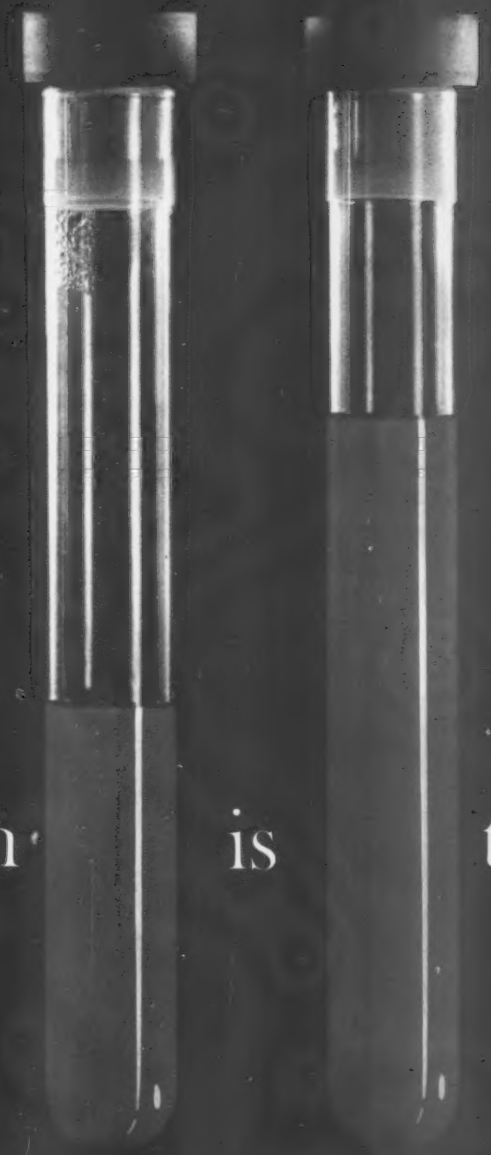

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*Rock, J.; García, C.-R., & Pincus, G.: *Am. J. Obst. & Gynec.* **79**:758, 1960. 41460

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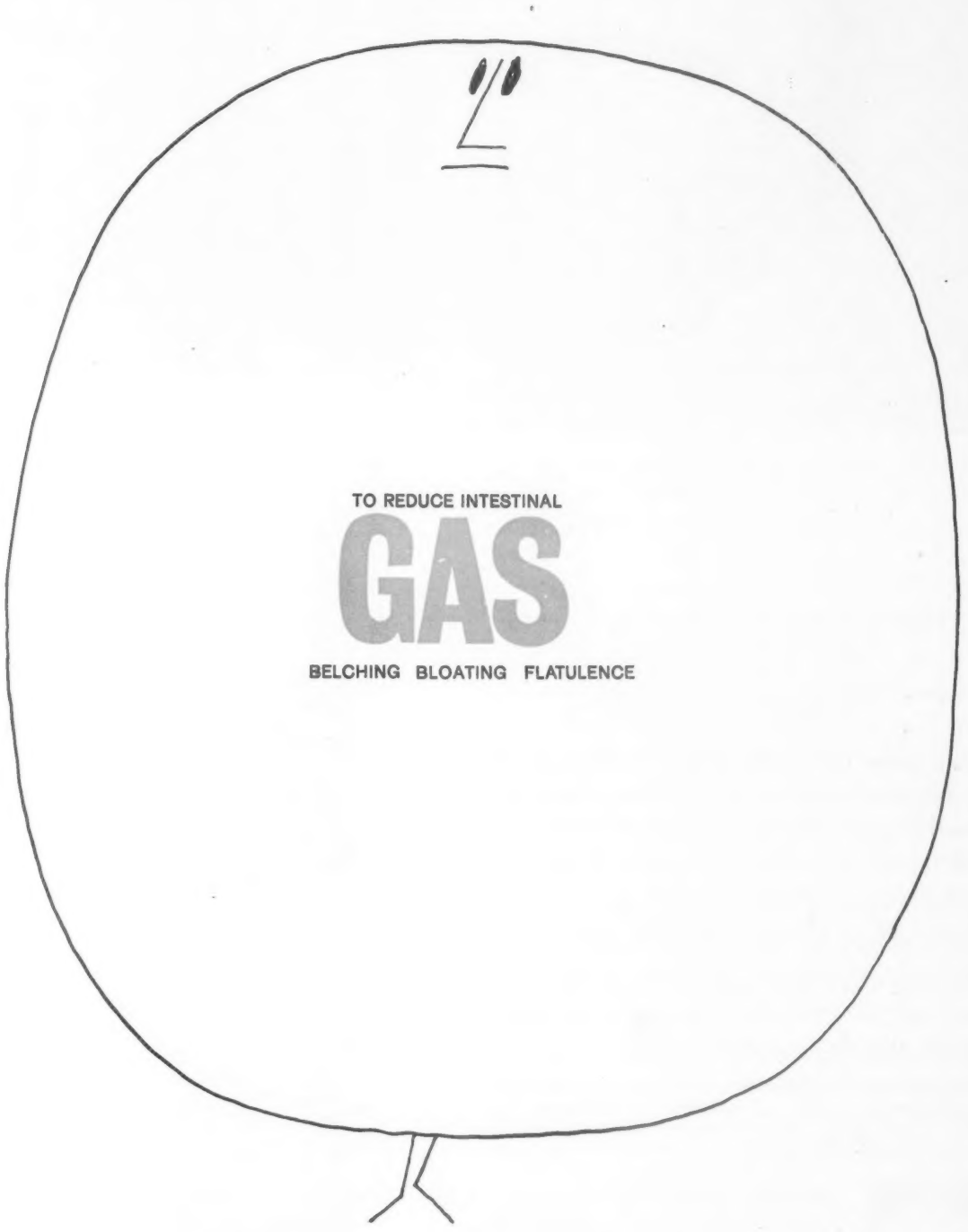

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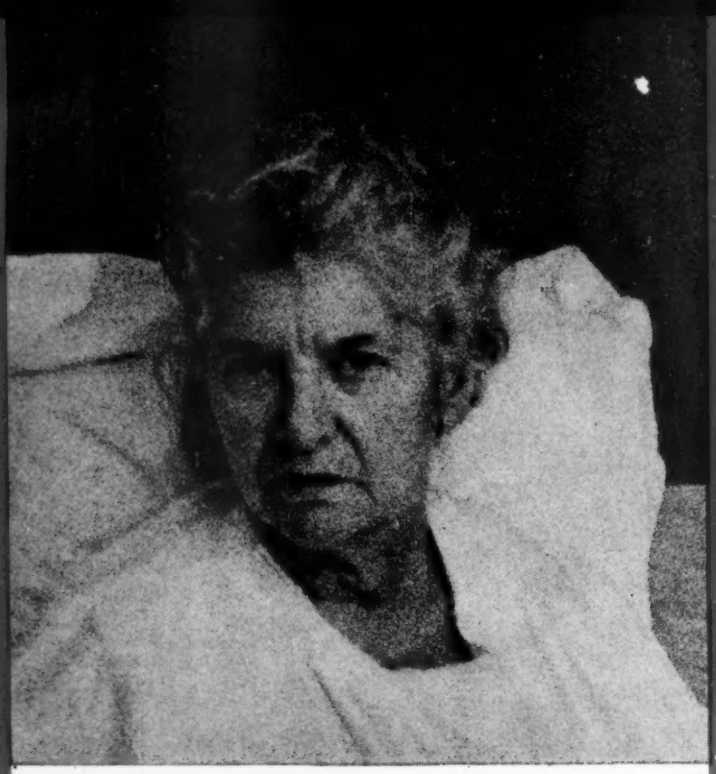

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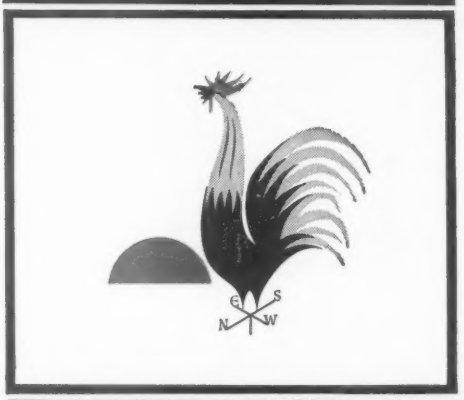

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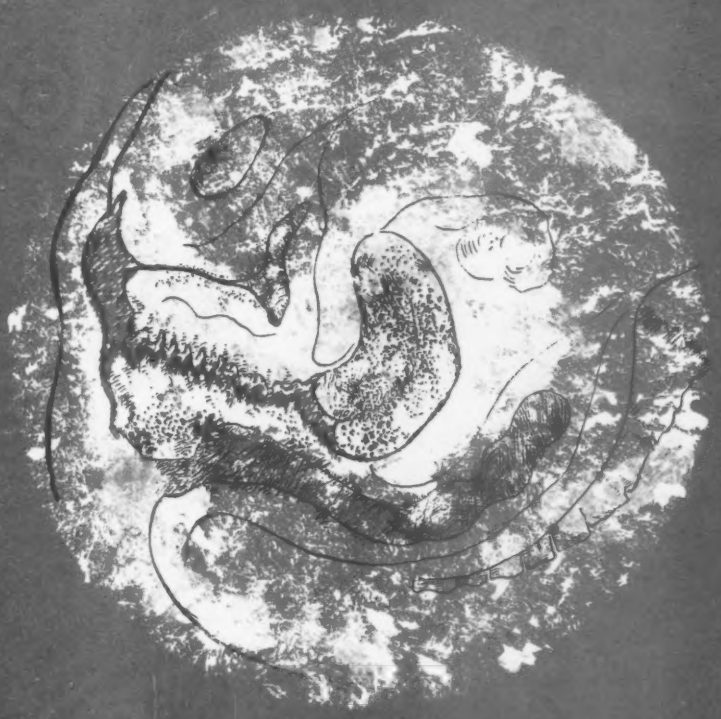

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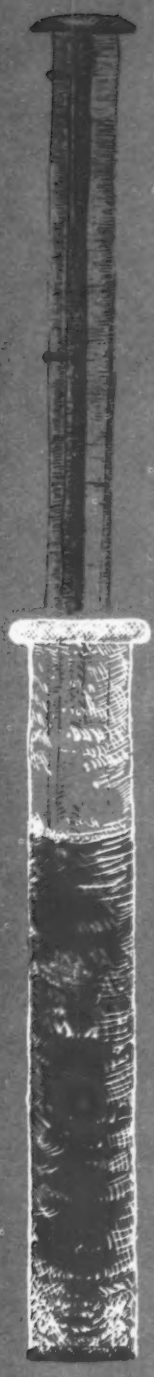

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in certain gynecologic complications... prompt symptomatic relief

Cervical Pathology	No. of Cases	Complete Healing	Partial Improvement	No Change
Nonspecific Cervicitis	27	24	3	0
Erosions	55	35	16	4
Lacerations	13	13	0	0
Postpartum Cervicitis	24	8	6	10
Electrocauterization of Cervix	10	9	1	0
Totals	129	89 (69%)	26 (20%)	14 (11%)

results of therapy with Elase[4]

INDICATIONS: *ELASE is of value in the treatment of vaginitis and cervicitis, as adjunctive treatment in cervical erosion... in surgical wounds... burns... chronic skin ulcerations... infected wounds... fistulas... sinus tracts... abscesses... hematomas... and ulcerative lesions of various types.*

CONTRAINDICATIONS: *ELASE is not recommended for parenteral use since the bovine fibrinolysin may be antigenic. There are no known contraindications to its topical use as recommended.*

PACKAGE INFORMATION: *ELASE, fibrinolysin and desoxyribonuclease, combined (bovine), Parke-Davis, is supplied in rubber diaphragm-capped vials of 30-cc. capacity. Each vial of ELASE as a lyophilized powder contains 25 units (Loomis) of fibrinolysin and 15,000 units of desoxyribonuclease. The contents of each vial may be reconstituted with 10 cc. of isotonic sodium chloride solution. Higher or lower concentrations can be prepared if desired by varying the amount of the diluent. To be maximally effective, the solution must be freshly prepared just prior to use.*

ELASE Ointment is supplied in 30-Gm. tubes, each containing 30 units of fibrinolysin and 20,000 units of desoxyribonuclease in a special petrolatum base. Six disposable vaginal applicators (V-Applicators) for instillation of ointment are available as a separate package. *Basic medical brochure available upon request.*

REFERENCES: *(1) Coon, W. W.; Wolfman, E. F., Jr.; Foote, J. A., & Hodgson, P. E.:* Am. J. Surg. **98**:4, *1959. (2) Friedman, E. A.; Little, W. A., & Sachtleben, M. R.:* Am. J. Obst. & Gynec. **79**:474, *1960. (3) Margulis, R. R., & Brush, B. E.:* Arch. Surg. **65**:511, *1952. (4) Personal Communications to the Department of Clinical Investigation, Parke, Davis & Company, 1959.*

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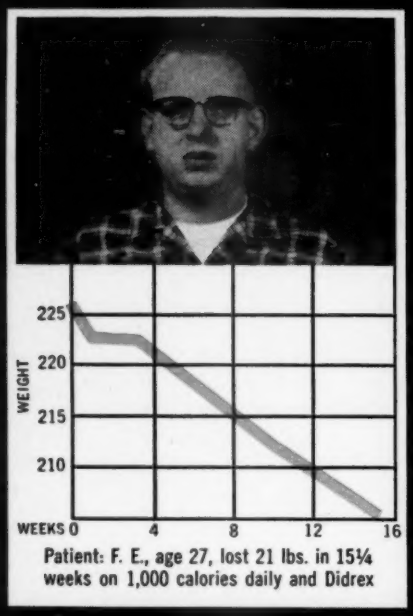
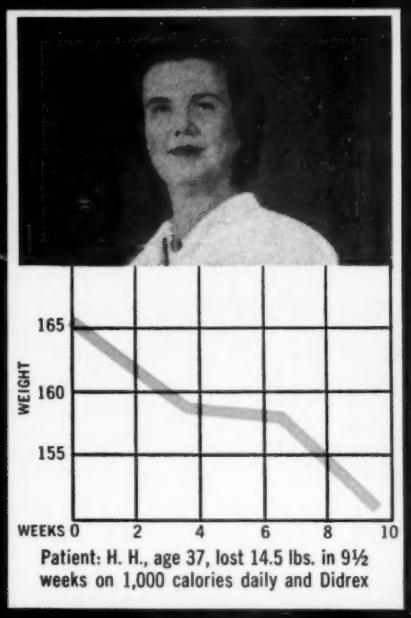
PARKE, DAVIS & COMPANY · Detroit 32, Michigan PARKE-DAVIS



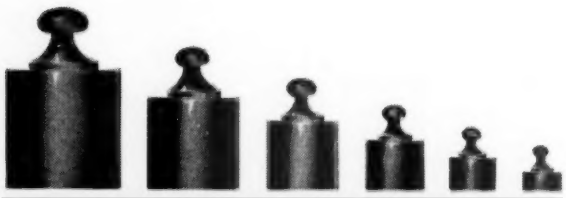
Patient: F. E., age 27, lost 21 lbs. in 15¼ weeks on 1,000 calories daily and Didrex



Patient: H. H., age 37, lost 14.5 lbs. in 9½ weeks on 1,000 calories daily and Didrex

Patient: A. P., age 34, lost 18.5 lbs. in 11½ weeks on 1,000 calories daily and Didrex

UPJOHN ANNOUNCES

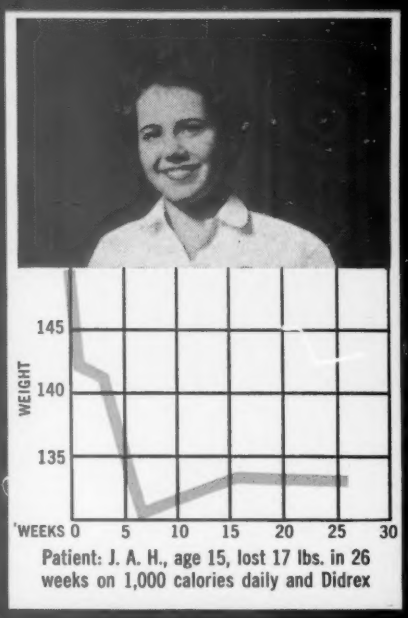


HELPS TAKE WEIGHT OFF. PERSISTENTLY

Didrex*

Patient: L. M., age 29, lost 20.5 lbs. in 9½ weeks on 1,000 calories daily and Didrex

Patient: P. M., age 41, lost 10.5 lbs. in 7¼ weeks on 1,000 calories daily and Didrex



Patient: J. A. H., age 15, lost 17 lbs. in 26 weeks on 1,000 calories daily and Didrex

in obesity management

PERSISTENT WEIGHT LOSS WEEK AFTER WEEK

Put it to your patient this way: The basic therapeutic objective of obesity management is to change dietary habits built over months or years of weight accumulation. This takes time and will. Consider Didrex, the new Upjohn appetite suppressant. Happily, it elevates mood which makes dieting more acceptable. More important, it works: "persistent significant weight loss" in patients followed for as long as 20 weeks. Added to your favorite reducing regimen, ½ to 1 Didrex tablet one to three times daily is usually adequate to preclude the "weight plateau" that so often discourages dieters after a few weeks. Available as 50 mg. tablets in bottles of 100. **Upjohn**

The Upjohn Company, Kalamazoo, Michigan

Photos and case histories courtesy Dr. Alan S. Rubinstein, Springfield, Illinois
*Trademark — brand of benzphetamine hydrochloride, UPJOHN

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N,α-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorexic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of obesity.

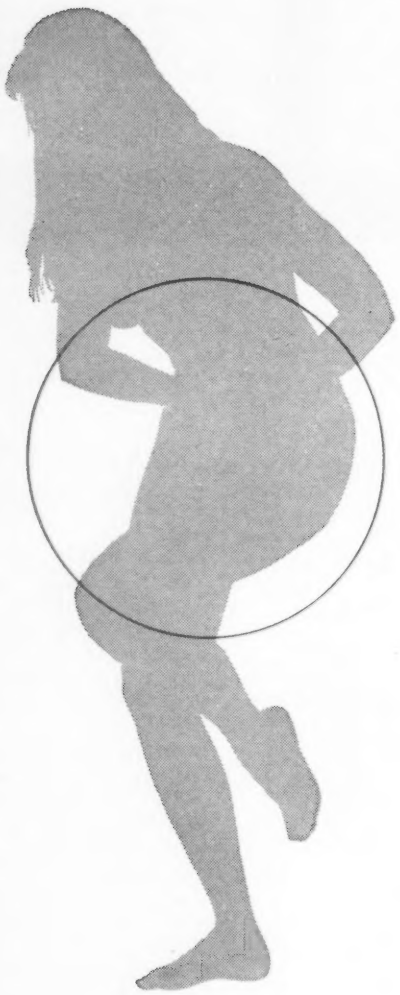
Contraindications: None known. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with ½ or 1 tablet (25 to 50 mg.) in midmorning for several days. Then adjust dosage to suit each patient's need to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects, similar to those reported from placebos, have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., press-coated, scored tablets, in bottles of 100.

in female urethritis referred pain complicates diagnosis



Pain in the groin, suprapubic region, thighs and lower back is often caused by urethritis but, as a result of negative urinary findings, is attributed to other organs. Direct examination of the urethra helps localize the origin of referred pain, evidence of urethral inflammation calling for local therapy.

Younger women with bacterial urethritis respond to the antibacterial, anesthetic and dilating effects of FURACIN Inserts (formerly FURACIN Urethral Suppositories) containing nitrofurazone 0.2% and the local anesthetic diperodon·HCl 2% in a water-dispersible base. Each suppository hermetically sealed in silver foil, box of 12.

Older women respond to the estrogenic, antibacterial, anesthetic and dilating effects of FURESTROL Suppositories containing, in addition to nitrofurazone and diperodon ·HCl, diethylstilbestrol 0.0077% (0.1 mg.) which corrects postmenopausal urethritis at the cellular level. Each suppository hermetically sealed in orchid foil, box of 12.

FURACIN® INSERTS and FURESTROL® SUPPOSITORIES

brand of nitrofurazone

alleviate pain—simplify treatment

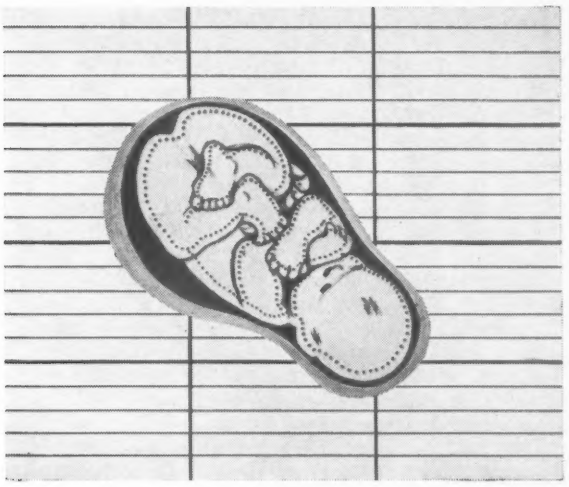
EATON LABORATORIES, NORWICH, NEW YORK

now in threatened premature delivery

Dactil®-OB

Brand of piperidolate hydrochloride, hesperidin complex and vitamin C

prolongs gestation / increases fetal survival rate



no intolerance / no endocrine disturbance / reduces need for bed rest

In a study of 618 pregnancies over a period of 4 years, premature births were reduced from 13.1% of 168 patients without Dactil to 4.7% of 450 patients with Dactil.* In the treated patients birth weights were increased.

Dosage: 1 tablet q.i.d. from the beginning of pregnancy in any patient with a history of previous difficulty. For more information send for Dactil-OB brochure.

*Stephens, L. J.: The Prevention of Premature Delivery, presented at the Pacific Coast Fertility Society, Las Vegas, Nevada, November 15, 1959.

72560

LAKESIDE

to encourage colonic peristalsis without whipping the bowel

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The active principle of Dorbane reaches the colon through the circulation. It acts directly and selectively upon the intrinsic plexus of the colon. The small bowel is not affected. Within 6 to 12 hours evacuation occurs without cramping or griping. Non-habituating. Each scored tablet of Dorbane contains 75 mg., and each teaspoonful of orange-flavored liquid contains 37.5 mg. of 1,8 dihydroxyanthraquinone. Suitable for patients of all ages.

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Dorbantyl Forte offers double strength dosage of the Dorbantyl combination for greater convenience and economy for patients requiring extra potency. In orange-and-gray capsules only.

Riker

Northridge, California

Eventually he'll learn. There are no "miracle" cures for dandruff. Selsun comes close, but there are possibly 5% that it won't help at all. But for the other 95%—and that probably includes this fellow—it's the most effective treatment available. Why not give him the word—and a prescription. You'll save him money down the drain.

SELSUN® Suspension an ethical answer to a medical problem

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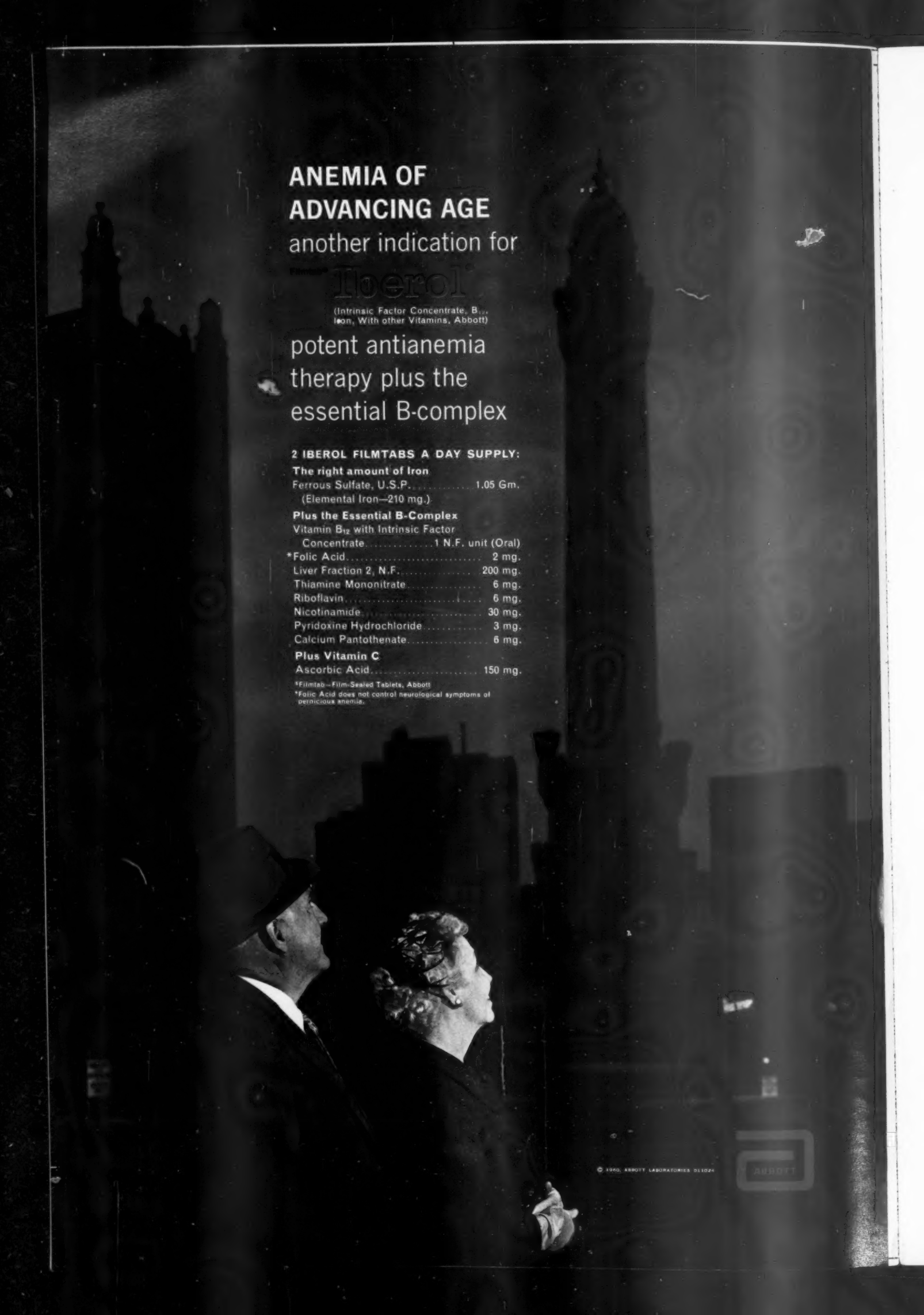
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The right amount of Iron
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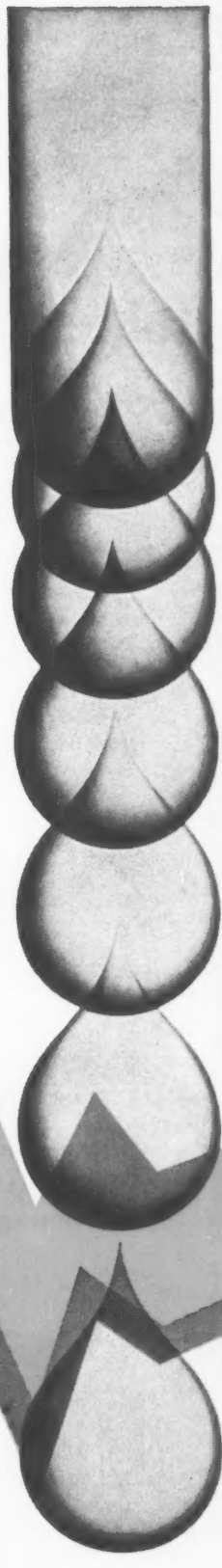
brand of chlorthalidone

longest in action... smoothest in effect

in hypertension and edema



greater loss of sodium
lesser loss of potassium

A new antihypertensive-saluretic, Hygroton, now enables still more effective control of hypertension and edema.

more evenly sustained therapeutic response
Because it is more prolonged in action than any other diuretic,[1] Hygroton affords a smoother, more evenly sustained response.

more nearly pure natriuretic effect
Hygroton produces only minimal potassium loss . . . affords a better sodium-potassium ratio than other saluretics.[3]

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As a rule, with Hygroton, restriction of dietary salt is unnecessary.

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For maintenance therapy three doses per week suffice to manage the vast majority of cases.[2]

in arterial hypertension
Sustained control without side reactions.

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Copious diuresis without electrolyte imbalance.

Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.

References:
(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr. 89:1126, 1959. (2) Fuchs, M., Res: et al.: Current Therap. Research 2:11, January, 1960. (3) Ford, R. V.: Manuscript submitted for publication.

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In threatened abortion...

Provera* is now available in a new long-acting injectable form:

ACTUAL SIZE

Formula:

Sterile micronized medroxyprogesterone acetate (17-alpha-hydroxy-6-alpha-methylprogesterone acetate).

Supplied:

In 1 cc. and 5 cc. size vials

REFERENCES: 1. Boschann, Hanns-Werner, and Drews, Renate, "The Effect of 6-alpha-methyl-17 alpha-acetoxyprogesterone on the Endometrium," Brook Lodge Symposium, Progesterone, 1960. in press. 2. Wied, George L., and Davis, M. Edward, Brook Lodge Symposium, Progesterone, 1960, in press.

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Depo-Provera**

Potent

Depo-Provera is 4 times as potent as any other available progestogen (by castrate assay).

Long-acting

A single 50 mg. injection of Depo-Provera will produce a progestational effect that lasts for up to 16 days.

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No significant untoward side effects have been reported.

More acceptable to patient

Micronized in sterile aqueous suspension—little or no pain at site of injection.

Depo-Provera

Upjohn

The Upjohn Company, Kalamazoo, Michigan

Control weight gain from test to term

Rx the anorexic with no reported contraindications

TENUATE suppresses appetite with no effect on heart rate, blood pressure, pulse or respiration,[1] no alteration of BMR.[2]

In a recent study of 105 patients who used diethylpropion (TENUATE) throughout their pregnancies,[3] the following effects on weight were recorded:

Actual loss of weight..... 7 patients
No gain in weight.....11 patients
Gain of less than 3 pounds per month....55 patients
Gain of more than 3 pounds per month..32 patients

DOSAGE: One 25 mg. Tablet one hour before meals, or 1 *new* TENUATE DOSPAN Tablet (75 mg.) daily, in midmorning, swallowed whole. An additional 25 mg. Tablet may be taken in midevening to control nighttime hunger.

SUPPLIED: TENUATE Tablets (25 mg. each), bottles of 100 and 1000; TENUATE DOSPAN Tablets (75 mg. each), bottles of 100.

REFERENCES: 1. Alfaro, R. D.; Gracanin, V., and Schlueter, E.: J. Lancet, *In press.* 2. Huels, G.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Nulsen, R. O.: Cur. Therap. Res. 2:102, 1960. 4. Horwitz, S.: Personal communication, 1959. 5. Spielman, A. D.: Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Ravetz, E.: Michigan Acad. Gen. Pract. Symposium, 1959. 7. Decina, L. J.: Exper. Med. & Surg., *In press.* 8. Scanlan, J. S.: Personal communication, 1959. 9. Kroetz and Storck: Personal communication. 1959.

TENUATE

(diethylpropion)

hunger control with less than 1% CNS stimulation[2,4-9]

Merrell SINCE 1828

THE WM. S. MERRELL COMPANY
Division of Richardson-Merrell Inc.
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NOW AVAILABLE—

TENUATE DOSPAN

10-12 HOUR HUNGER CONTROL WITH 1 TABLET

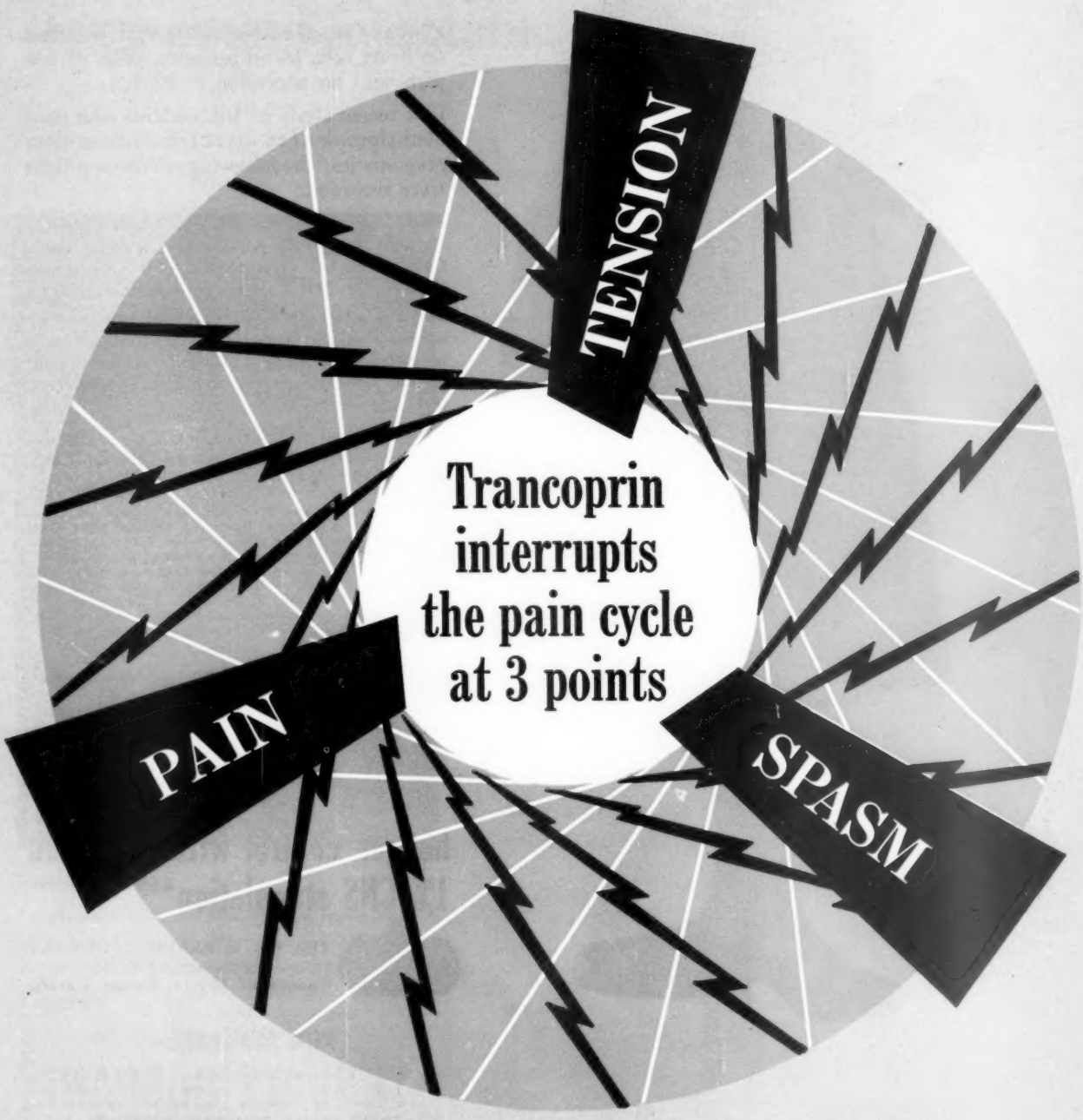
TRADEMARKS: TENUATE®, DOSPAN® (MERRELL'S CONTINUOUS RELEASE DOSAGE FORM)

announcing...

Trancoprin®

acetylsalicylic acid (300 mg.) and chlormezanone (50 mg.)

Tablets



a broad spectrum non-narcotic analgesic

Trancoprin, a new analgesic, not only raises the pain perception threshold but, through its chlormezanone component, also relaxes skeletal muscle spasm[1-6] and quiets the psyche.[2,3-5,7]

The effectiveness of Trancoprin has been demonstrated clinically[8] in a number of patients with a wide variety of painful disorders ranging from headache, dysmenorrhea and lumbago to arthritis and sciatica. In a series of 862 patients,[8] Trancoprin brought excellent or good relief of pain to 88 per cent of the group. In another series,[9] Trancoprin was administered in an industrial dispensary to 61 patients with headache, bursitis, neuritis or arthritis. The excellent results obtained prompted the prediction that Trancoprin "... will prove a valuable and safe drug for the industrial physician."[9]

Exceptionally Safe

No serious side effects have been encountered with Trancoprin. Of 923 patients treated with Trancoprin, only 22 (2.4 per cent) experienced any side effects.[8,9] In every instance, these reactions, which included temporary gastric distress, weakness or sedation, were mild and easily reversed.

Indications

Trancoprin is recommended for more comprehensive control of the pain complex (pain → tension → spasm) in those disorders in which tension and spasm are complicating factors, such as: headaches, including tension headaches / premenstrual tension and dysmenorrhea / low back pain, sciatica, lumbago / musculoskeletal pain associated with strains or sprains, myositis, fibrositis, bursitis, trauma, disc syndrome and myalgia / arthritis (rheumatoid or hypertrophic) / torticollis / neuralgia.

Dosage

The usual adult dosage is 2 Trancoprin tablets three or four times daily. The dosage for children from 5 to 12 years of age is 1 tablet three or four times daily. Trancoprin is so well tolerated that it may be taken on an empty stomach for quickest effect. The relief of symptoms is apparent in from fifteen to thirty minutes after administration and may last up to six hours or longer.

How Supplied

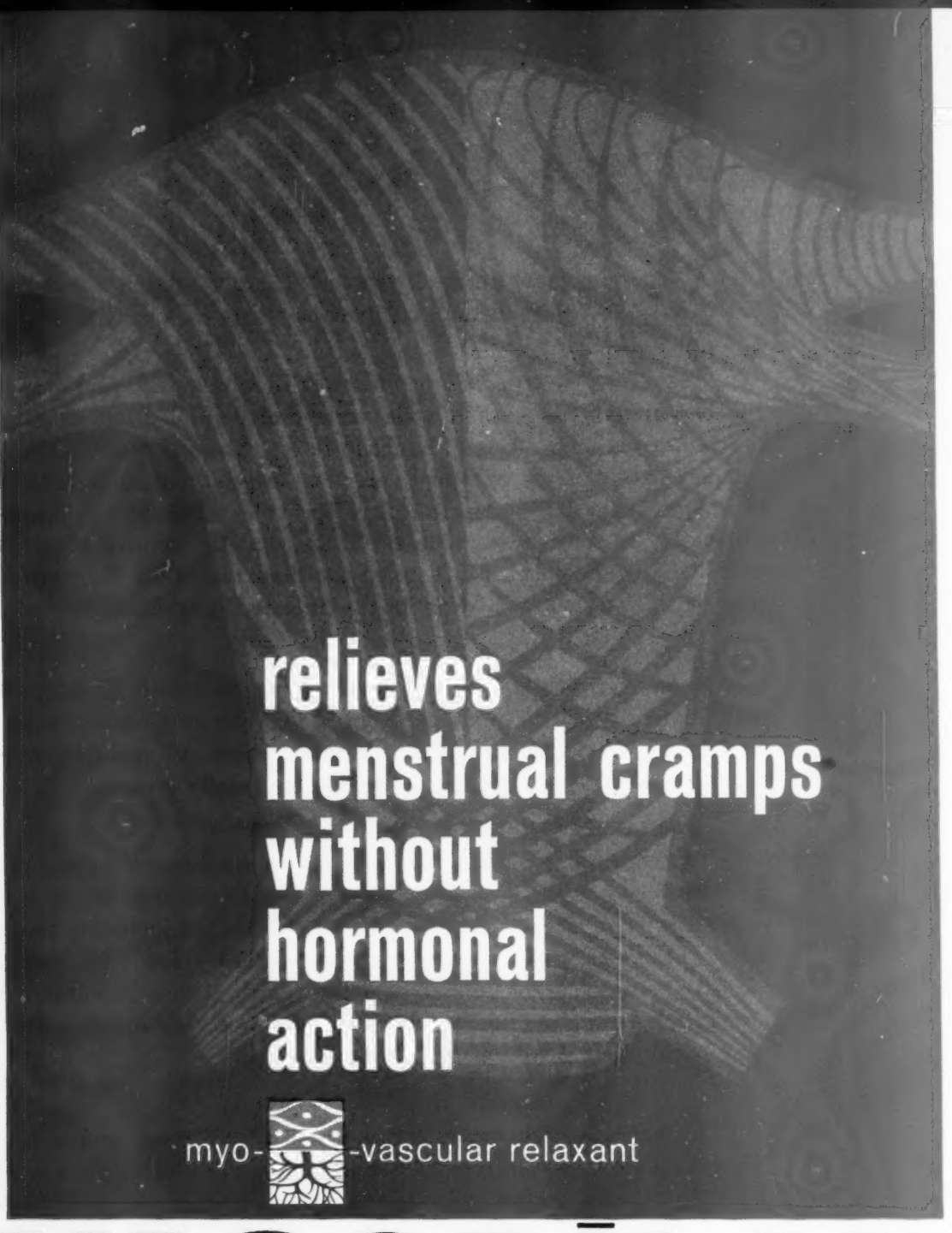
Each Trancoprin tablet contains 300 mg. (5 grains) of acetylsalicylic acid and 50 mg. of chlormezanone [Trancopal® brand]. Bottles of 100 and 1000.

Trancoprin Tablets / **non-narcotic analgesic**

References: 1. DeNyse, D. L.: *M. Times* 87:1512, Nov., 1959. 2. Ganz, S. E.: *J. Indiana M. A.* 52:1134, July, 1959. 3. Gruenberg, Friedrich: *Current Therap. Res.* 2:1, Jan., 1960. 4. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960. 5. Lichtman, A. L.: *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 6. Mullin, W. G., and Epifano, Leonard: *Am. Pract. & Digest Treat.* 10:1743, Oct., 1959. 7. Shanaphy, J. F.: *Current Therap. Res.* 1:59, Oct., 1959. 8. Collective Study, Department of Medical Research, Winthrop Laboratories. 9. Hergesheimer, L. H.: An evaluation of a muscle relaxant (Trancopal) alone and with aspirin (Trancoprin) in an industrial medical practice, Ibid.

Winthrop LABORATORIES, New York 18, N. Y.

Trancoprin and Trancopal (brand of chlormezanone) trademarks reg. U. S. Pat. Off.



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Isoxsuprine hydrochloride, Mead Johnson

relieves uterine spasm and hypermotility by *direct* relaxant action on uterine muscle*

proved effective clinically with a low incidence of side effects*

dosage: For menstrual cramps, give 10 or 20 mg. (1 or 2 tablets) three or four times daily 24 to 72 hours prior to expected onset of menstruation. Continue until pain has been averted.

supplied: 10 mg. tablets, bottles of 100; 2 cc. ampuls (5 mg./cc.) for *intramuscular* use, boxes of 6.

*Voulgaris, D. M.: Obst. & Gynec. *15*:220-222 (Feb.) 1960.

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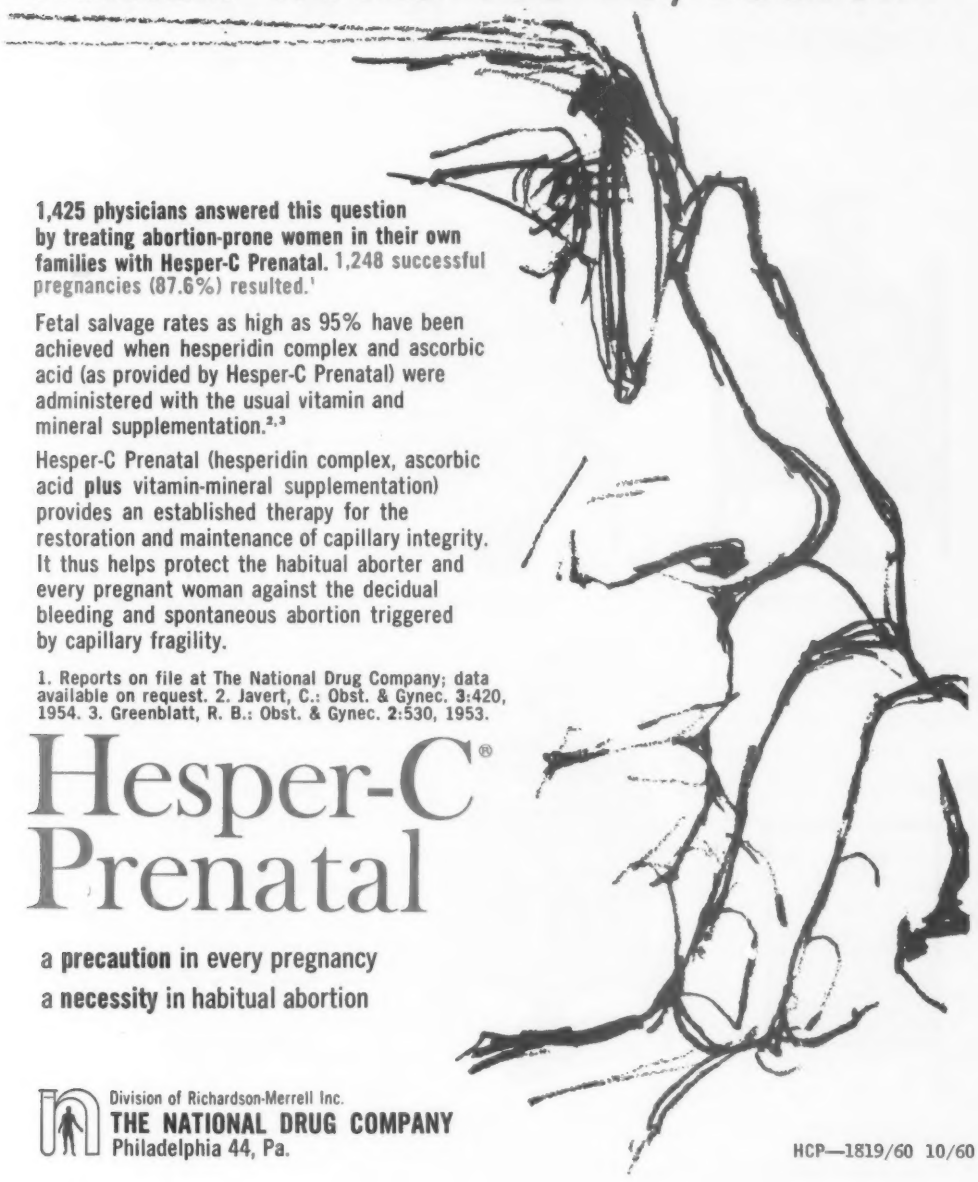
Symbol of service in medicine

IF YOUR OWN WIFE WERE A SPONTANEOUS ABORTER ...WHAT WOULD YOU DO, DOCTOR?



1,425 physicians answered this question by treating abortion-prone women in their own families with Hesper-C Prenatal. 1,248 successful pregnancies (87.6%) resulted.[1]

Fetal salvage rates as high as 95% have been achieved when hesperidin complex and ascorbic acid (as provided by Hesper-C Prenatal) were administered with the usual vitamin and mineral supplementation.[2,3]

Hesper-C Prenatal (hesperidin complex, ascorbic acid **plus** vitamin-mineral supplementation) provides an established therapy for the restoration and maintenance of capillary integrity. It thus helps protect the habitual aborter and every pregnant woman against the decidual bleeding and spontaneous abortion triggered by capillary fragility.

1. Reports on file at The National Drug Company; data available on request. 2. Javert, C.: Obst. & Gynec. 3:420, 1954. 3. Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

Hesper-C® Prenatal

a **precaution** in every pregnancy
a **necessity** in habitual abortion

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anemia... "silent partner" of so many clinical conditions...

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volume 80 *number* 6
December 1960

American Journal of Obstetrics and Gynecology

GYNECOLOGY

Effect of audiogenic stimulation on genital function and reproduction

BERNHARD ZONDEK, M.D.
ISACHAR TAMARI
Jerusalem, Israel

SEXUAL function depends not only upon an adequate endocrine balance but also upon environmental factors. It is well known that climatic conditions play a considerable role. Exposure of male animals, for instance, to cold and heat results in involution of the testes and the main accessory organs with complete cessation of spermatogenesis—according to Selye,[1] a systemic stress picture. The female sex organs undergo a similar reaction resulting in disturbances of the estrus cycle and ovarian atrophy. In Israel, where immigration from many countries is so prevalent, we are often confronted with amenorrhea of several months' duration, frequently associated with slight hirsutism and gain in weight, in young girls unaccustomed to the subtropical climate of the Mediterranean coast. Dempsey and Searles[2] found that simultaneous exposure to cold and light produced persistent estrus in rats as well as stimulation of the adrenals and the thyroid. It is known that hens lay a greater number of eggs under conditions of continuous light. Arvay and associates[3] applied intensive noise, light, and electric stimuli to rats, whereby catatonic conditions were observed in the majority of animals. They observed increased luteinization of the ovaries, accompanied by cessation of the estrus rhythm (diestrus) and severe degenerative changes of the follicular apparatus, the ovaries, and the vegetative nerves of the ovary.

To what extent sexual function can be influenced by means of the sense organs presents a problem which we have been studying during the past few years. Our approach has been the exposure of rodents

From the Hormone Research Laboratory, the Hebrew University–Hadassah Medical School.

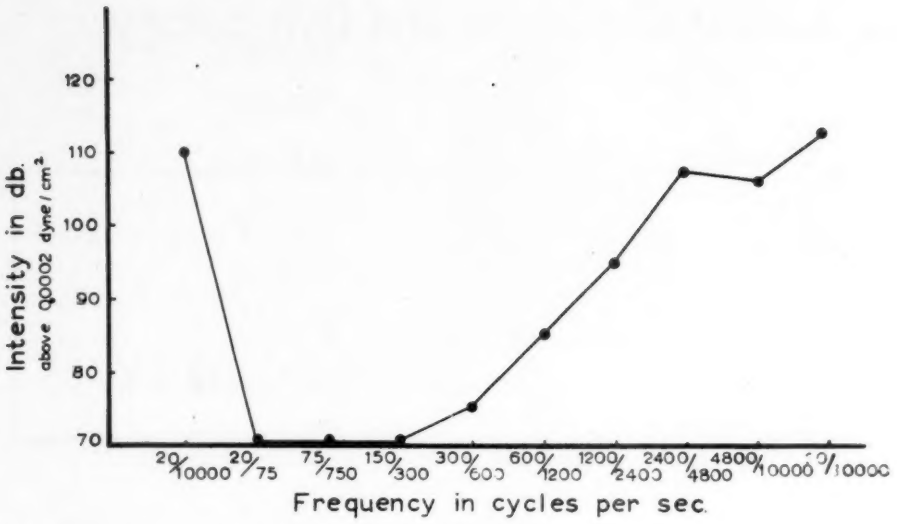


Fig. 1. Sound spectrum of the electric bell.

to auditory stimuli. Miline and his co-workers[4, 5] believe that auditory stimulation may be unique in its effect on neuroendocrine interrelations. Studies reported so far indicate that audiogenic stimuli induce changes resembling those produced by other stressful stimuli. The weight of the adrenal cortex increases under audiogenic stimulation[6] combined with an increase of corticosteroids.[7] The studies of Sackler and associates[8] also provide considerable evidence of increased production of adrenocorticosteroids, increased ascorbic acid content of the adrenals, further inhibition of gonadotropic and ovarian hormones, and possible inhibition of thyrotropic and thyroid hormones. Biró and co-workers[9] conclude that the sound stimulus in part evokes the usual change in the pituitary-adrenocortical system characteristic of systemic stress, but in part inhibits the eosinopenic stress effect.

Effect of audiogenic stimuli on ovarian function

Our experiments on rodents tend to show that audiogenic stimuli do not evoke regressive changes in the genital organs and in their functions, but stimulate the gonadotropic activity of the anterior pituitary lobe.

The experiments were carried out on batches of infantile and mature female and male rats of the Hebrew University strain and on mature female rabbits which were kept isolated for at least one month before the start of the experiments. The animals were kept close to an electric bell which rang for periods of one minute at 10 minute intervals, day and night. The characteristics of this sound—analyzed by a General Radio noise level meter and an octave band analyzer—were as follows: (a) the over-all sound intensity was of about 110 decibels above 0.0002 dyne per square centimeter; (b) the sound intensity was not equal in all frequencies; the low frequencies were around 70 decibels and the high frequencies (4,800 and above) were around 110 decibels. The exact sound spectrum is demonstrated in Fig. 1. Some of the rats reacted quite soon, showing unrest, increased motor activity, and running around in circles, whereas most did not react at all. We did not notice convulsions as other authors[3, 10, 11] have described. After some time the rats became accustomed to the sound stimuli and were quiet. Rabbits were not influenced in their behavior.

Experiments on rats. Thirty mature rats, weighing 180 to 200 grams, reacted to the continual sound stimuli after 1 to 2 weeks, by changes in the estrus rhythm, presenting as prolonged or sometimes persistent estrus.

After 60 days of stimulation the sexual organs showed the following picture: the uteri were somewhat increased in weight, 703 mg. as against 528 mg. in the controls. The ovaries were enlarged, their weight varying from 40 to 130 mg., whereas the weight of the controls ranged between 30 and 70 mg.; the average was 83 mg. compared with 51 mg. in the controls. The ovaries were composed essentially of corpora lutea, which were exceptionally large, their activity being manifested by a rich vascularization. The number of corpora lutea varied in different experimental animals from 8 to over 20, whereas in the controls 6 to 10 were found. The ovaries contained fewer mature follicles than those of the controls, but the maturation of the follicle was not completely arrested and ova were preserved.[12, 13]

The enlargement of the ovaries (62.7 per cent weight increase) with a considerable increase in the number of corpora lutea indicates the stimulating effect of sound on the anterior pituitary gland and the consequent release of gonadotropin. These findings speak against the assumption of a systemic stress reaction, which is manifested by atrophy of the sex organs due to inhibition of anterior pituitary gonadotropic function.

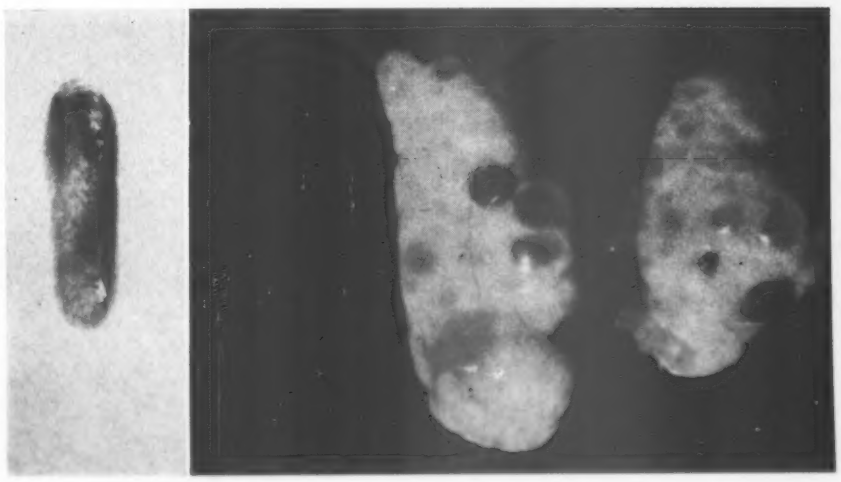
It is worthy of note that the adrenals in the experimental animals exposed to audiogenic stimuli during 60 days were also enlarged, averaging 61.5 mg. as compared with 39.5 mg. in the controls.

In the next experiments we tried to stimulate gonadotropic function in immature animals.

Infantile 3-week-old mice, weighing 6 to 8 grams (as used for the Aschheim-Zondek test), were exposed for 96 hours to audiogenic stimuli. The results were negative, and neither estrus nor the formation of corpora lutea were evoked.

Premature sexual development could not be achieved. Sixteen infantile, 5-week-old rats were exposed to the bell ringing and the start of the estrus reaction determined by daily vaginal smears. After 18 to 20 days the estrus reaction occurred with formation of corpora lutea. In 16 control rats the same results were obtained, indicating no functional difference between the treated and untreated rats. There was, however, a difference in the weight of the ovaries—16.6 milligrams in the controls and 30 milligrams in the experimental animals.

Sixty-seven infantile 3- to 4-week-old rats, weighing 30 to 35 grams, were exposed 3 to 24 hours to stimulation of the auditory organs and killed 24 hours after the start of



A *B*

Fig. 2. Rabbit 44. Effect of 14 days of audiogenic stimulation—ovaries enlarged threefold *(B)*. Many large follicles, two of them filled with blood (blood points APR-II). Galactorrhea. *A*, Control; *B*, experimental rat. (×3.)

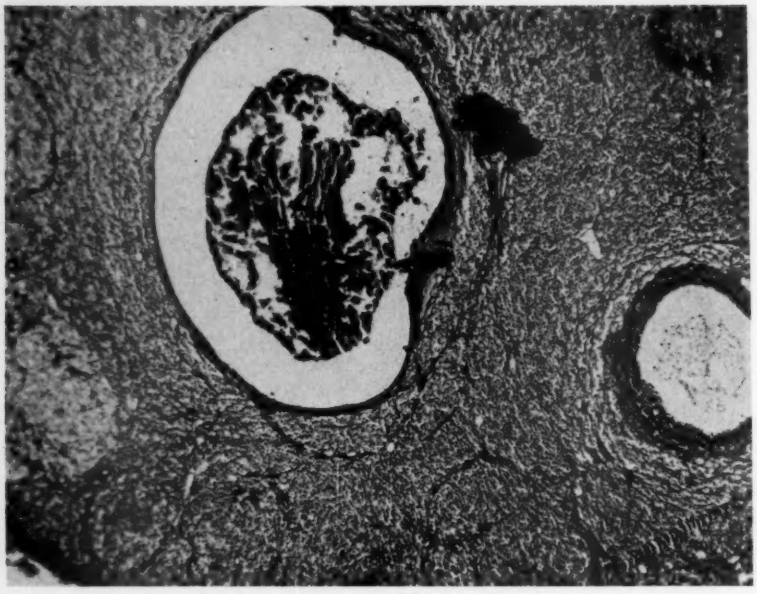


Fig. 3. Rabbit 44 (cf. Fig. 2). Large follicle with hematoma (blood point APR-II). (×30; reduced 1/9.)

the experiment. Twenty-four of 67 (35.8 per cent) animals showed some ovarian hyperemia, but not quite so distinct as after injection of human pregnancy urine.

The experiments show that sound stimulation causes an increase of the anterior pituitary gonadotropic reaction in adult rats. In immature animals, however, where gonadotropic function has still not started, audiogenic stimulation apparently has no or little effect.

In infantile and mature male rats no distinct stimulating effect on the sex organs could be achieved by continual audiogenic stimuli. There was no distinct inhibitory action, either on the weight of the testes and the accessory organs or on spermatogenesis. Miline[14] reported that male rats exposed to noise stimuli develop retarded spermatogenesis, oligospermia, and hyperplasia of the interstitial cells.

Experiments on rabbits. The stimulating effect of audiogenic stimuli on anterior pituitary gonadotropic function was demon-

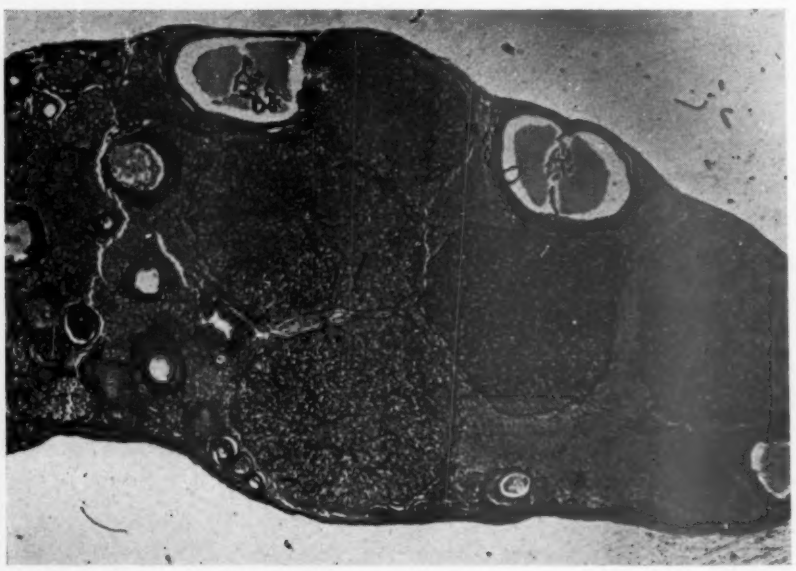


Fig. 4. Rabbit 46. Twenty-two days of audiogenic stimulation. Ovary contains small and enlarged follicles and 5 corpora lutea (APR-III). (×33.)

strated even more convincingly on mature rabbits. Animals kept separated for at least one month neither ovulate nor produce corpora lutea. For ovulation to occur, the hypothalamus requires stimulation either by coitus or by electric impulse.[15] Gonadotropic reactions,[16-19] follicle hematoma (Reaction II), and the formation of corpora lutea (Reaction III) can be obtained in rabbits by gonadotropic hormones derived from the anterior pituitary lobe or from human pregnancy urine.

Experiments were carried out on 48 mature rabbits with an average weight of 2,200 grams which were kept isolated for at least one month. In some animals the state of the ovaries was controlled by laparotomy before the start of the experiment. The rabbits were exposed to the auditory stimuli for from 6 to 60 days. In 16 of 48 rabbits, a positive result was obtained. The weight of the ovaries was increased to 385 milligrams as compared with 205 milligrams in the controls.* The ovaries contained small and large follicles, several of them with follicle hematomas (blood points) and one or several corpora lutea—changes we have described as indicative of gonadotropic reactions[16-19] (Figs. 2-5). Very characteristic and easily recognizable by the naked eye were the dark blue raised blood points. It was found possible by auditory stimuli to simulate a positive pregnancy test (Friedman) in the rabbit.

With gonadotropin we can obtain a positive reaction on rabbits' ovaries in nearly 100 per cent of cases. In the present sound stimulation experiments, however, only one third of the rabbits reacted, for which result we can offer no explanation. The duration of stimulation does not seem to play a decisive role. In 1 rabbit we obtained a positive result after 6 days of stimulation; of 10 animals stimulated 13 to 15 days 4 reacted positive; of 8 rabbits stimulated 23 days, 5 showed a positive reaction. After 57 days 3 out of 4 rabbits reacted positively.

In 6 of the 16 positive cases another noteworthy effect took place—the enlargement of the mammae with accompanying galactorrhea, as in pregnancy.

The important point of these experiments seems to be the principle that by audiogenic stimuli we are able to induce the same changes as by administration of pituitary or chorionic gonadotropin.

Effect of audiogenic stimuli on fertility

Impairment of fertility. In marked contrast to the stimulating effect of audiogenic stimuli on female genital function is the inhibitory action on the course of pregnancy. In control experiments the fertility rate of our strain of rats was determined over a period of 14 months. Ten to 15 couples—each animal weighing 180 to 200 grams—were mated monthly, in separate cages, for 4 days without prior determination of the state of the estrus cycle. The fertility rate for this 4 day period in 190 rats ranged between 70 and 100 per cent with an average of 77.8 per cent. The 190 rats produced 911 offspring, making an average of 6.5 young per rat.

Fig. 5. Rabbit 95. Extreme effect of audiogenic stimulation. Ovary contains 5 blood points and 10 corpora lutea (APR-II and III). (×4; reduced ⅙.)

In the first experiments 10 couples were housed together each month for 7 months and exposed to auditory stimuli for 14 to 26 days. The fertility was greatly diminished, only 4 of 70 rats producing 28 offspring, making an average litter of 2.5 per rat. The controls during the 7 months showed a fer-

*In 4 rabbits the weight of the ovaries was even more than 600 milligrams, three times the control rate.

Table I. Inhibitory effect of auditory stimuli on fertility in rats

Stimulation (days)	*Rats*	*Pregnancies*	*Offspring*
0	70	56	473
14-26	70	4	28
0	20	14	120
4	20	1	4 (in resorption?)

tility rate of 80 per cent with 473 young. Thus, the fertility rate was diminished from 80 to 5.7 per cent of pregnancies and the number of offspring to 5.9 per cent of the control rate. These experiments show the remarkable inhibitory effect that sound stimuli have upon fertility (Table I).

In a further experiment, mating and sound stimulation time were reduced to 4 days and the rats were killed on the sixteenth day of the experiment. Among the 20 animals only 1 was found to be pregnant, and the 4 fetuses were considerably diminished in size as compared with the controls. Among 20 controls 14 (70 per cent) were pregnant with 120 fetuses. The fertility rate in this experiment was thus reduced to 7.1 per cent and the number of offspring to 3.3 per cent of the control rate (Table I).

The question arises as to whether the impairment of fertility is due to a male or a female factor. It might be possible that the sound stimulus induces an irritability of the male partner disturbing his mating reactions. We thought of investigating this possibility by searching daily vaginal smears for spermatozoa. We did not, however, apply this method so as not to introduce another factor apart from sound which may have disturbed female sexual behavior and the course of pregnancy. In some experimental animals we did find spermatozoa. Furthermore, in every experiment a small proportion of the rats became pregnant showing that mating was occurring. In further studies we are now checking for the presence of spermatozoa in the vagina.

To get further insight into the mechanism of audiogenically induced infertility we exposed 20 mature males and 20 females separately to the sound stimulus for 7 to 9 days. After stopping the auditory stimulation each male was housed together with an unexposed female and every female with an unexposed male. After 4 days' mating time they were separated and were sacrificed 12 days later. The purpose of this experiment was to determine whether the audiogenic stimulus induces anatomical changes in the sex organs (degeneration of the ovum, oligospermia, etc.). If this were the case, female animals exposed for some days to the stimulation would fail to conceive and male animals would be unable to fertilize the ova. The results were as follows:

The fertility of both females and males exposed to the audiogenic stimuli proved to be impaired. The fertility rate in the females was reduced in one experiment to 12.5 per cent and in another to 37.5 per cent. Surprisingly, the fertility of the males was also reduced to 12.5 per cent. From these preliminary experiments it seems that in both males and females the reproductive mechanism is adversely affected by audiogenic stimuli. Whether this is a behavioral response or an organic or functional effect remains to be seen.

Disturbance of the course of pregnancy. Auditory stimuli induce infertility. The following experiments show that stimulation of the auditory organs can disturb the course of pregnancy.

In the control experiment 20 mature rats were housed with male partners—each couple in a separate cage—for 4 days, and the males then separated from the females. Pregnancy occurred in 16 animals (80 per cent), and 125 offspring were delivered. After mating for 4 days, similar groups of female rats were exposed to auditory stimuli for 48 hours from the fourth or the sixth day until the eighth or the tenth day (Table II). Stimulation during the fourth to the sixth day resulted in a decline in fertility from 80 to 25 per cent. The effect is most pronounced following stimulation from the eighth to the tenth day, whereby fertility is decreased 93.8 per cent (from 20 rats only 1

animal delivered). Whereas the controls were delivered of 6.2 fetuses per animal, in the exposed rats the index decreases to 0.5 per animal. These results were confirmed in a further experiment with 40 mature rats. The conditions were the same, but the animals were killed on the sixteenth day of the experiment: (a) of 20 rats stimulated for 48 hours on the fifth to the seventh day only 2 proved to be pregnant (10 per cent with 2 fetuses; (b) of 20 rats stimulated for 48 hours on the eighth to the tenth day, 2 were pregnant, whereas in 3 the development of the fetuses was disturbed.

Both experiments demonstrate that pregnancy is adversely affected by audiogenic stimuli. Whether the auditory stimulus inhibits implantation or whether other factors are involved is not yet clear to us. It seems that the mechanism of implantation is disturbed in some way since the inhibitory effect is most pronounced on the seventh to the tenth day of the experiment, at the time when the blastocyst should be implanting. Studies being carried out at present may give a better insight into this question. We have also to take into consideration the possibility of an effect on the uterine musculature, inducing hypermotility, resulting in expulsion of the ovum from the uterine cavity.

Our studies so far indicate that stimulation of the acoustic nerve induces, probably via the hypothalamus, stimulation of anterior pituitary gonadotropic function, manifested by persistent estrus, formation of corpora lutea, and follicle hematomas. In contrast to this stimulating effect, the auditory stimuli induce infertility and interfere with the course of established pregnancy.

Summary

1. Exposure to stimulation of the auditory organs in mature rats stimulates the anterior pituitary gonadotropic function, manifested by prolonged or persistent estrus, enlargement of the ovaries, and increase of the corpora lutea in number and size.

2. In immature rats, where gonadotropic function has still not started, audiogenic stimulation has apparently little or no effect. Premature sexual development could not be achieved. Hyperemia reaction of the ovaries, however, but not so distinct as that following injection of gonadotropin, could be induced in about one third of the experimental animals.

3. The stimulating effect of audiogenic stimuli on anterior pituitary gonadotropic function was demonstrated convincingly on mature rabbits. In animals kept isolated for at least one month the following changes were observed: enlargement of the ovaries, follicle hematomas (blood points, APR-II), and formation of corpora lutea (APR-III). In a few cases galactorrhea was induced.

4. In contrast to the stimulating effect of auditory stimuli on female genital function is the inhibitory action on fertility. In control groups the fertility rate was 77.8 per cent with an average of 6.5 young per rat. Audiogenic stimulation reduced the fertility rate from 80 to 5.7 per cent of pregnancies and

Table II. Inhibitory effect of audiogenic stimuli on the course of pregnancy

Rats	*Mating (days)*	*Auditory stimuli (days)*	*Pregnancies*	*%*	*No. fetuses*	*No. per rat*
20	4	Control	16	80	125	6.2
20	4	4-6 (96-144 hours)	5	25	31	1.5
20	4	6-8 (144-192 hours)	8	40	63	3.1
20	4	7-9 (168-216 hours)	3	15	15	0.75
20	4	8-10	1	5	10	0.5

to 5.9 per cent with relation to the number of offspring.

5. After mating for 4 days the rats were exposed to audiogenic stimuli during the fourth to sixth days, seventh to ninth days, or eighth to tenth days. In the control group the fertility rate was 80 per cent. The stimulated animals showed a decline to 25, 15, and 5 per cent, respectively. Whereas the controls were delivered of 6.2 fetuses per animal, in the exposed rats the index decreases to 0.5 per animal.

6. Auditory stimuli induce infertility and interfere with the course of established pregnancy. Whether the auditory stimulus inhibits the implantation of the fertilized egg or whether other factors are involved must be clarified by further studies.

We are indebted to Professor A. Laufer, Department of Pathology, for his help, and to Dr. P. Jordan, Tel Aviv, for determining the sound spectrum of the electric bell used in our experiments.

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Ovulation time

A modified rat hyperemia test compared with other criteria

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A TEST for determining ovulation time utilizing the rat hyperemia reaction was reported by Farris[1] in 1946. This required the collection of daily morning urine specimens from women undergoing fertility studies. The technique consisted of injecting 2 c.c. of early morning urine subcutaneously into 22-day-old 40 to 60 gram female Wistar rats. After 2 hours, these rats were sacrificed by means of illuminating gas and the degree of ovarian hyperemia was measured by means of a Munsell color chart. Farris reported that his test was extremely accurate in predicting ovulation. This was proved clinically by means of insemination and resultant pregnancy. Corner, Farris, and Corner[2] corroborated the accuracy of the rat hyperemia test. However, other investigators[3-6] have been unsuccessful in their attempts to repeat these experiments. For example, in 1949, Levin, Buxton, and Engle[3] reported on the validity of the Farris test. They obtained negative results in 7 patients studied, 3 of whom were subjected to laparotomy for verification of ovulation.

Our interest in the rat hyperemia test began when Behrman,[7] utilizing a modified technique, reported that there was a substance excreted in the urine near midcycle which induced hyperemia in the ovary of the immature rat. He further stated that this substance was LH (luteinizing hormone) as proved by the African weaver bird reaction.[8] This species of the Finch family undergoes a distinct change in its plumage at the mating season. This change in plumage can be induced by the injection of LH.

The purpose of this presentation is to evaluate this modified rat hyperemia test and to compare it with other selected criteria of ovulation.

Material and method

Observations on a group of 69 infertile patients during 130 cycles (Table I) form the basis for this report. These patients were instructed to collect daily morning urine samples beginning shortly after the cessation of the menstrual period. They were warned to restrict their fluid intake after 6 P.M. the night before and to refrain from ingestion of alcoholic beverages.

Table I. Categories of patients studied

	Patients	*Cycles*
Artificial insemination	31	70
Routine infertility	29	51
Culdoscopy	9	9
Total	69	130

The Behrman modification of the rat hyperemia test was utilized: 3 c.c. of urine was injected intraperitoneally into each of two 40 to 50 gram immature female rats. These rats were of a local Wistar or the

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Presented before a meeting of the Chicago Gynecological Society, May 15, 1959.

Sprague-Dawley strain. The rats were sacrificed with chloroform within 4 hours of injection. An incandescent lamp was used for lighting. The presence of definite hyperemia in one or more of the rats' ovaries was used to indicate a positive reaction. This was recorded as a strong positive, weak positive, or negative reaction. The end point of this test is similar to that obtained in the rat pregnancy test as reported by Kelso[9] and others.[10-13]

These patients were seen daily in our office until the majority of our own criteria for ovulation had been satisfied. These included observations of the basal body temperatures taken rectally, cervical mucorrhea and spinnbarkeit, and vaginal smear cornification. Our technique of cervical mucus evaluation has been previously described.[14] The vaginal smears were stained by the rapid Schorr method and the degree of vaginal cornification estimated.

Results

Table II shows a comparison of various criteria of ovulation in a group of patients successfully inseminated. In this select group of patients there was excellent correlation between the low point in the basal body temperature curve, maximal spinnbarkeit, vaginal smear cornification, and the rat hyperemia test. Donor inseminations were performed once or twice in these successful cycles.

Table III shows a comparison of the rat hyperemia test with other criteria of ovula-

Table II. Comparison of various criteria of ovulation in a group of patients successfully inseminated*

No.	Basal body temperature low point	Spinnbarkeit	Vaginal smear	Rat test	Artificial insemination	Comment
016	13†	14	14	12, 13	14	
037	13	11	11, 12	11	11, 13	
957	20	20	20	20	18, 20	Missed abortion
981	18	18	18	17	16, 18	
1507	?	14	14	12	14	Missed abortion
1774	13	13	14	14	14	
1823	19	18	19	20	19	
1873	15	13	?	11, 14	13	
2065	13	14	13, 14	14	11, 14	
183	18	18, 19	19	19	18, 19	

*Basal body temperature low point: day of the low point before the rise; spinnbarkeit: day of maximal stretch phenomenon; vaginal smear: day of maximal cornification; rat test: day of maximal ovarian hyperemia.

†Numbers refer to day or days of cycle.

Table III. Comparison of the rat hyperemia test with other criteria of ovulation confirmed at culdoscopy*

No.	Basal body temperature low point	Menses	Spinnbarkeit	Vaginal smear	Rat test	Culdoscopy	Findings
045	13†	28	15	18	19	19	Corpus hemorrhagicum
715	14	30	13	17	15	22	Corpus luteum
911	9	21	0	0	10	14	Corpus luteum
915	12	?	10	12	12, 13	17	Corpus luteum
1828	?	32	14, 15	0	15, 16	16	No evidence of ovulation
1854	?	?	16	16	17	18	Corpus hemorrhagicum
1865	10	28	11	12	14	14	Corpus hemorrhagicum
1945	15	32	14	14	13	16	Extensive adhesions
3101	15	26	14	14	13	20	Corpus luteum

*Basal body temperature low point: low point before the sustained rise; menses: day of cycle when menstruation began; spinnbarkeit: maximal spinnbarkeit; vaginal smear: a cornified smear.

†Numbers refer to day or days of cycle.

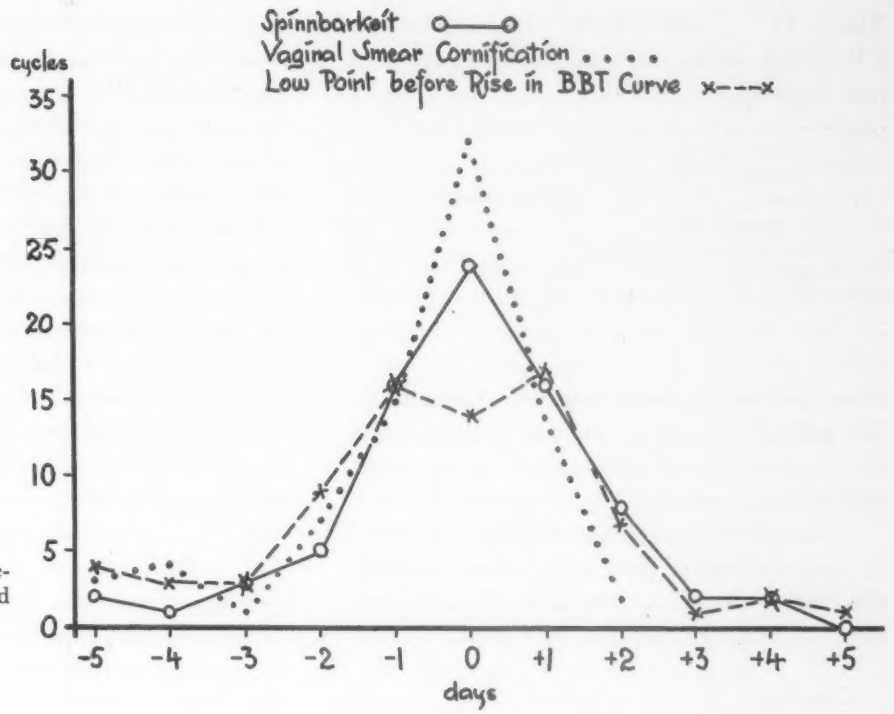

Fig. 1. Correlation between the rat test and spinnbarkeit.

tion confirmed at culdoscopy. Corpora lutea were visualized in 7 of the 9 patients observed. In Case 1828 both ovaries were well visualized and no evidence of a recent corpus luteum was found. In Case 1945 extensive adhesions obscured both ovaries. In Cases 1854, 1945, and 3101 there was excellent correlation between the rat test and our clinical signs of ovulation time.

Fig. 1 graphically shows how the rat test compared with other criteria of ovulation in the entire group of 69 patients observed during 130 cycles. Those cycles in each method of ovulation timing wherein the test was either negative or nondiagnostic had to be deleted. In the remaining cycles, the day of the positive rat test was compared with the day of ovulation as determined by the low point in the basal body temperature curve, spinnbarkeit, and vaginal smear cornification. Zero day indicates those cycles in which the positive rat test occurred on the same day when the other criteria were positive. The minus side of the graph indicates those cycles wherein the other criteria of ovulation occurred from one to 5 days prior to the positive rat test. The plus side indicates those cycles when the other criteria were positive after the positive rat test.

When the low point in the basal body temperature curve was compared with the day of the positive rat test, there were 63 cycles out of 81 with good correlation within plus 2 to minus 2 days. Seventeen cycles were deleted because the low point before the rise was poorly defined or absent. Further, there were 29 cycles deleted because the rat test was consistently negative and 3 additional cycles in which multiple positive reactions occurred. There remained 81 cycles which could be compared.

When maximal spinnbarkeit was compared with the rat test, there were 69 cycles out of 81 with good correlation within minus 2 to plus 2 days. The same 29 negative rat test cycles, the 3 additional cycles with multiple positive reactions, and the 17 cycles in which no mucorrhea occurred had to be deleted.

The cornified vaginal smear correlated with the rat test within minus 2 to plus 2 days in 70 cycles out of 78. As in the above two categories, there were the same 29 neg-

Table IV. Cycles during which various criteria of ovulation time were negative or nondiagnostic

17	Absent spinnbarkeit
21	Nondiagnostic vaginal smears
17	Poorly defined low point in basal body temperature
29	Inconclusive rat tests
3	Multiple positive rat tests

ative rat cycles and 3 cycles in which multiple positive reactions occurred. There were 21 cycles in which the vaginal smear could not be interpreted.

Table IV indicates the number of cycles in each method of ovulation timing wherein the test was either negative or nondiagnostic and hence could not be used.

Comment

The validity of the Farris test as a diagnostic aid in predicting ovulation time has been challenged by some observers. Utilizing a modified technique, however, we were able to detect positive reactions indicating presumptive ovulation time in better than 75 per cent of the cycles tested. The modifications employed differed from Farris' original technique in: (1) the employment of 3 c.c. of urine instead of 2 c.c.; (2) the site of injection was intraperitoneal instead of subcutaneous; (3) the reaction was read in 4 hours instead of 2 hours; (4) the rats were sacrificed with chloroform rather than with illuminating gas; (5) although a local Wistar strain was used initially in our work, we later found the Sprague-Dawley strain more responsive; (6) the end point of this test, observed with incandescent light, was a very definite ovarian hyperemia as compared to the control animals (the Munsell color chart was not used).

Because of the modifications employed in this test, our results cannot be compared with those of Farris. His reported results are much better, but apparently his technique cannot be duplicated in other laboratories.

In the prediction of impending ovulation, our most valuable clinical test depends upon the outpouring of clear, thin, cervical mucus with the characteristic stretch phenomenon or spinnbarkeit. The observations on cervical mucus are practical, and they are easily performed in office practice. Those patients who do not show this outpouring of cervical mucus either have anovulatory cycles or endocervical glands refractory to estrogenic stimulation.

The vaginal smear technique is valuable as a rough assay of estrogen-progesterone activity. Inasmuch as training and experience are required to interpret changes in the smear incidental to ovulation, the smear test cannot be recommended as a simple aid in the detection of ovulation.

Most physicians rely upon the interpretation of the basal body temperature chart for ovulation timing. We have found the day to day fluctuations of the basal body temperature difficult to evaluate until an entire cycle has been recorded.

The best test of ovulation is conception. When we follow a group of patients who become pregnant after donor insemination, we are better able to evaluate tests of ovulation. Table II demonstrates how well all the criteria of ovulation corelated in the group of patients who conceived. This is in contrast to the larger group of patients undergoing routine infertility studies wherein many of these criteria frequently failed to appear or were nondiagnostic. In this latter group but few pregnancies resulted.

Inasmuch as we do not breed our own rats, we had to rely upon commercial sources. These animals were available to us only twice weekly, so that it became necessary to store the daily urine samples under refrigeration for as long as 4 days. Refrigeration for this period of time apparently had no effect upon these specimens. However, a test of ovulation available only twice weekly is impractical, so that we did rely upon our other criteria in the management of the patient. Storing of the urine samples did make it possible for our technician to run a sequence of tests at one time on each individual patient. For example, the urine

from a patient collected on Days 10, 11, 12, and 13 of a cycle could be injected into 4 pairs of rats at the same time. After 4 hours when these rats were explored, the day to day variation in ovarian hyperemia could be compared and the day of optimal response ascertained. Otherwise, we did experience some difficulty in determining gradations of ovarian hyperemia.

Out of the 130 test cycles, there were 29 cycles wherein all the rat tests were negative. In these 29 cycles, no conceptions occurred and none of these patients was examined with the culdoscope for evidence of corpus luteum formation. Therefore, these 29 cycles could represent absent or abnormal ovulation.

In our opinion, the importance of the Farris reaction, as well as Behrman's modification of the test, is to call attention to a detectable quantity of hormone, perhaps LH, appearing in the urine at midcycle. If this spurt of LH could be determined chemically rather than biologically, it would obviate the dilemma of groping for a good test of ovulation.

Summary and conclusions

1. The rat test was compared with other criteria for determination of ovulation time in 69 infertility patients during 130 cycles. The rat test correlated best with vaginal smear cornification.

2. There were 32 cycles in which the rat test was nondiagnostic. There were 17 cycles in which the low point in the basal body temperature was poorly defined. Twenty-one vaginal smear cycles could not be accurately read. Poor mucorrhea with absent spinnbarkeit occurred during 17 cycles.

3. In the group of 31 patients undergoing artificial insemination observed during 70 cycles, there were a total of 10 pregnancies. In this group of 10 patients, there was excellent correlation between the rat tests and the other criteria of ovulation time.

4. This modified rat hyperemia test as performed in our laboratory cannot be recommended for routine ovulation timing. It does indicate, however, that there is a substance excreted in the urine at midcycle, which is probably LH.

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Discussion

Dr. S. J. Behrman, Ann Arbor, Michigan. Dr. Dresner states that he was able to obtain positive responses to the Farris test for ovulation using the Sprague-Dawley and Wistar rats. In our laboratory we have been able to obtain the same results with Eli strains. In addition, we have run FSH, estrogen, and LH tests, using the African weaver finch, every 2 days throughout the cycle and correlated this with the modified hyperemia test. In 90 per cent of our series, the modified hyperemia test was positive at the time of ovulation as correlated with the vaginal smear, spinnbarkeit, and occasionally culdoscopy. Seventeen of 40 artificial inseminations with a single

injection technique were successful with this method.

I am in full agreement with Dr. Dresner that the hyperemia test is not a practical one for the man in practice. Furthermore, I believe that it is not so much a test of ovulation as one for the *prediction* of ovulation. By this I mean that one usually gets a weak positive reaction the day before the test shows a strong positive. In doing artificial insemination one can make an appointment for the day following the first positive response, when a single insemination will be done at the optimum time. The hyperemia test is a reflection of the peak of LH or ICSH hormone at the time of ovulation.

Finally, I am impressed with the lack of correlation between the various methods of detecting ovulation (Papanicolaou smear, spinnbarkeit, hormone analysis, hyperemia test) and the basal body temperature chart. I am still unable to correlate ovulation with either the low point, mid-point, or high point of the thermal shift—and therefore do not believe that the temperature chart is of any use in the *prediction* of ovulation, but solely in a retrospective survey to determine whether or not ovulation has occurred.

DR. COHEN (Closing). Dr. Behrman's results demonstrate that the rat ovarian hyperemia test in his hands gives a close correlation with vaginal smear cytology for the time of ovulation. There was rather poor correlation with the basal body temperature curve, but Dr. Behrman does not believe that one can pinpoint ovulation by means of the basal body temperature curve.

I instruct my patients to take their basal body temperatures daily. I do not know whether ovulation occurs a day or two prior to the low point, at the low point, or on the rise from low to high. However, when I find that the basal body temperature has been elevated for 48 hours, I am sure that ovulation has already occurred. Therefore, the patient need not report any longer for observation during that current cycle.

Present tests of ovulation timing are tedious and perhaps not too accurate. A simple and accurate test for ovulation is certainly most worthy of further research.

Human cervical epithelial changes produced by podophyllin

HAROLD A. KAMINETZKY, M.D.
Chicago, Illinois

DYSPLASTIC lesions of the cervix constitute a serious clinical problem. They may be found adjacent to in situ or invasive cancer. On the other hand, they may exfoliate malignant appearing cells when there is no cancer. Therefore, treatment has not been standardized and remains empirical.

The lesions included under the designation, "cervical dysplasia" or "atypical epithelial hyperplasia," may follow variable courses. In some patients they remain unchanged or disappear entirely. In others they become progressively more atypical. It is even thought they may develop into in situ or invasive cancer, but this assumption remains unproved. Moreover, it is impossible to predict the potential of any particular lesion from current morphologic criteria. Finally, it seems possible that abnormal tissues and cells of malignant appearance can be produced by various stimuli unrelated to the process of carcinogenesis. Trichomonas infection and pregnancy are said to be such stimuli. Experiments testing these hypotheses are in process or projected.

Following the experiments of King and his co-workers,[5-8] Saphir[10] applied podophyllin to the cervices of patients prior to hysterectomy. He reported changes resembling carcinoma in situ in the squamous epithelium. McGrew and I[4] undertook the study of the histologic and cytologic effects of podophyllin applied to the cervices of mice. We found this substance was capable of inducing changes in the cervix resembling atypical epithelial hyperplasia. Such lesions exfoliated and cells examined by the Papanicolaou technique were often indistinguishable from those shed by squamous carcinoma. Our experiments and those of others [1, 2, 3, 9] who utilized skin as a target organ indicate that neither podophyllin nor its partition products is carcinogenic. In order to test rigorously the potential of podophyllin as a carcinogen, we are currently painting the cervices of 50 mice three times a week for an entire year. To date, after 6 months, we have not produced a single cervical cancer although the animals continue to shed malignant appearing cells.

From the Department of Obstetrics and Gynecology, College of Medicine, University of Illinois.

Aided by a grant from the American Cancer Society.

Presented at a meeting of the Chicago Gynecological Society, Dec. 18, 1959.

Material

Forty-four women were included in this study. All required hysterectomy for conditions unrelated to cervical disease. The most frequent indications for hysterectomy were chronic pelvic inflammatory disease, prolapse, and leiomyomas. No patient with malignancy or suspicion of malignancy was included in this group. No postmenopausal patients were found suitable for this study.

Method

The posterior lip of the cervix was selected as the target for podophyllin and biopsy specimens were obtained 3 weeks

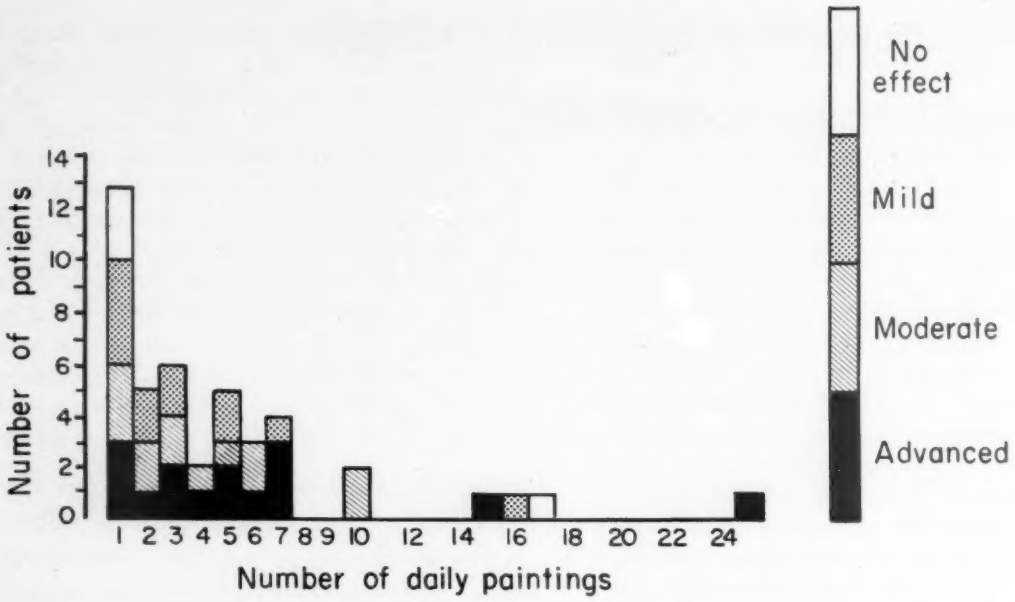

Fig. 1. Histologic effect of podophyllin.

before the patient's admission to the hospital. The anterior lip provided the control. More than half of the patients had four-quadrant biopsies. A cervical smear and a vaginal smear were also prepared at this time. No patient was included in the study in whom biopsy showed atypia or whose smear contained suspicious cells. As expected, most specimens had evidence of chronic cervicitis.

Painting was begun after the patient was hospitalized. Ten per cent podophyllin in mineral oil was applied to the entire posterior lip including the area of the squamocolumnar junction. An attempt was made

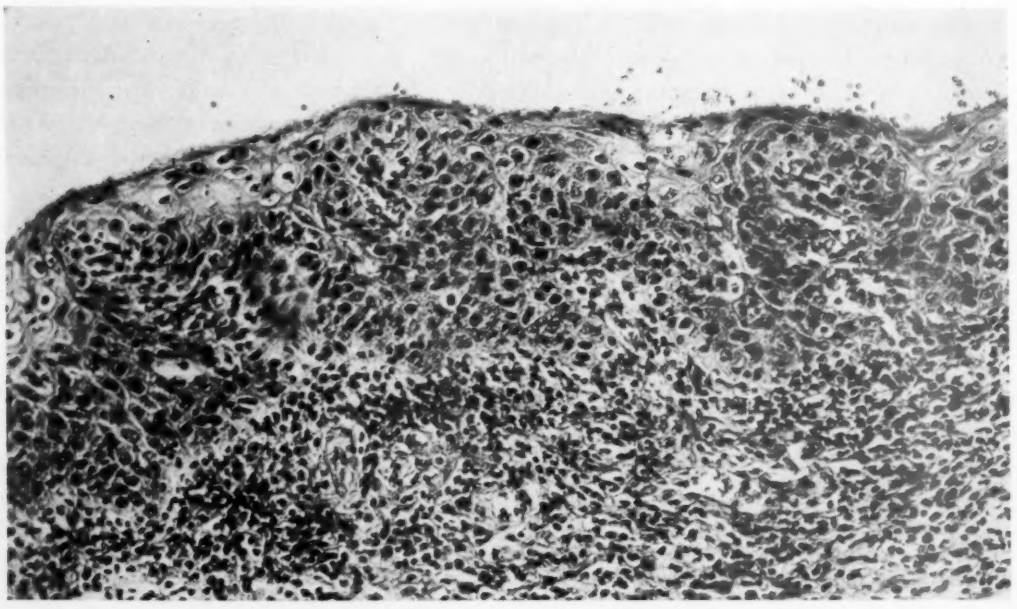

Fig. 2. Marked inflammation after two podophyllin applications. Hypercellularity and some disorganization of the epithelium may represent intense pre-existing cervicitis, but the vacuolization and areas of rather marked nuclear pleomorphism are probably due to podophyllin. (×250; reduced ¼.)

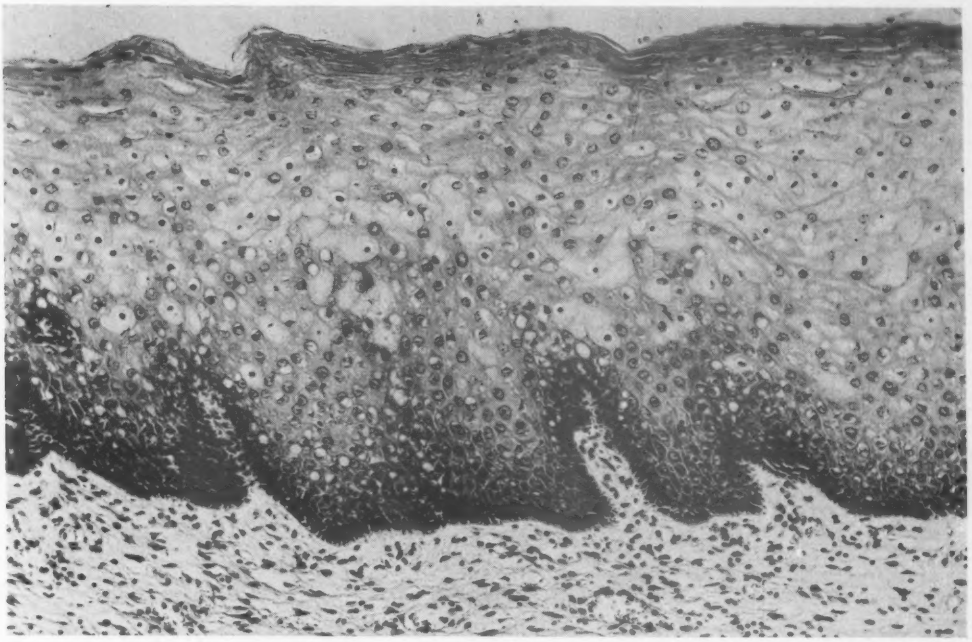

Fig. 3. Moderate epithelial change observed after seven applications. Basal cell crowding and irregularity reflect increased mitotic activity. Characteristic degeneration vacuoles are noted in all layers. (×250; reduced ¼.)

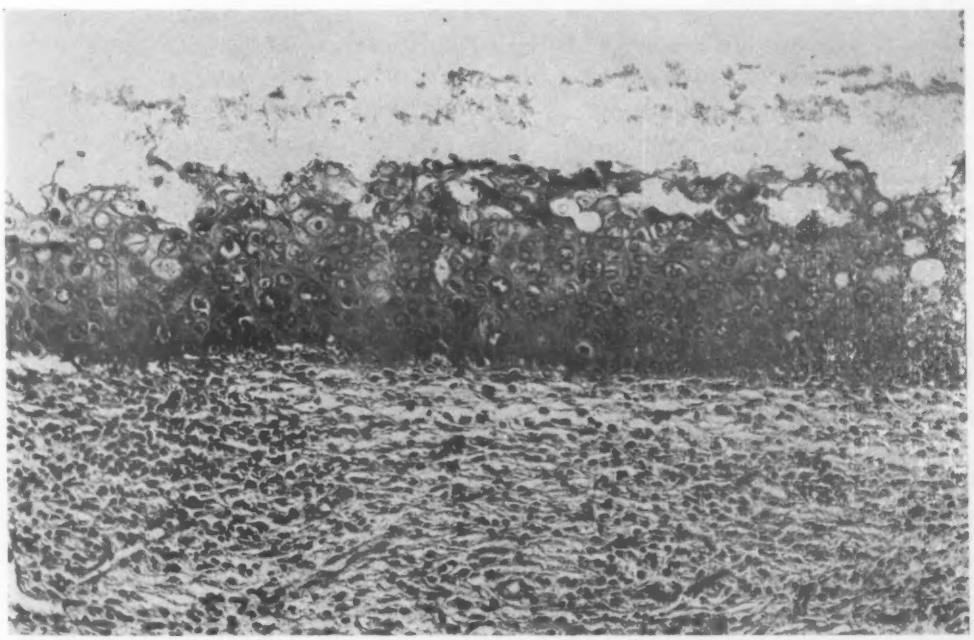

Fig. 4. Dysplasia observed in another patient after seven paintings. Basal and parabasal mitoses are present. There are scattered vacuolated cells. Atypical cells occupy most of the epithelium. (×250; reduced ¼.)

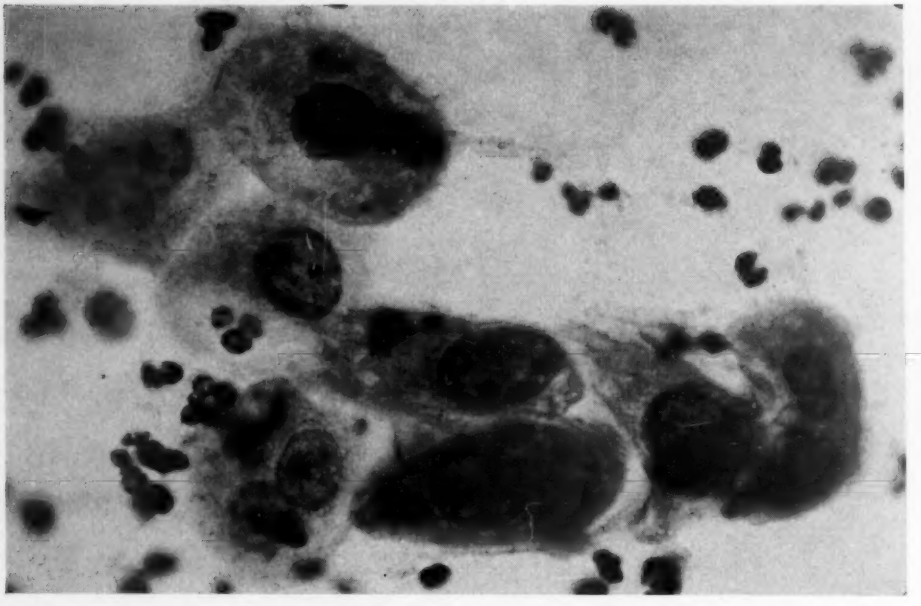

Fig. 5. Squamous cells from intermediate layer of epithelium (15 podophyllin applications). There is variation in size and shape of cells and nuclei, nuclear and nucleolar enlargement, and binucleation. (×700; reduced ⅓.)

to exclude the anterior lip from contact with the podophyllin; however, in the region of the squamocolumnar junction this was not always possible. Painting was carried out once a day, and new smears were prepared prior to each painting. Hysterectomy was performed at various intervals depending on a number of uncontrolled variables and by whatever route best served the requirements of the underlying pathologic process. Three sections were usually prepared from the posterior lip of the cervix and two from the anterior lip.

Results

Grossly evident inflammation of the posterior lip of the cervix and the adjacent vaginal mucosa was noted after one or two applications of podophyllin. Increased quantities of cervical mucus were produced by most patients. There were no complaints of irritation. At operation the vaginal mucosa was somewhat friable because of the chemical inflammation. On the other hand, this did not cause any problem of cuff healing or noticeable postoperative irritation of the peritoneum. No persistent cytologic abnormality was found in patients seen 6 weeks after hysterectomy.

The histologic effects of podophyllin are graphically portrayed in Fig. 1. Suspicious or malignant appearing cells were recovered from 12 of the 44 women. In one the cervix was painted only once, in two it was painted 3 times, in two 5 times, in one 6, in one 7,

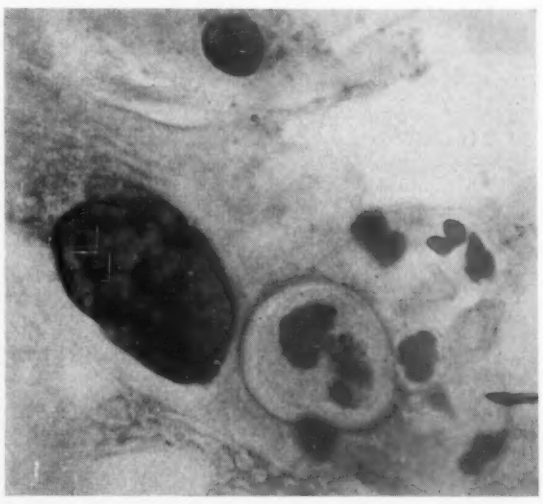

Fig. 6. Giant basophilic squamous cell containing a small eosinophilic prematurely cornified cell; nuclei are both abnormal. Seen in a cervical smear after 25 applications of podophyllin. (×900; reduced ⅓.)

in two 10, in one 15, in one 17, and in one 25 times. Curiously, one patient whose cervix was painted 16 times produced only slightly distorted cells. Certainly this was not the rule. Seven patients had mild changes in smears and 4 others showed moderate effect. There were, in addition, 20 patients from whom no atypical cells were recovered, 11 of these having had but a single podophyllin application. On the other hand, there was advanced atypia in the histologic specimens of 3 patients painted only once. In 25 patients histologic atypia was more advanced than the corresponding cytologic change. However, the opposite was true in 7 patients. One patient, whose cervix was painted 17 times and whose smears contained malignant appearing cells, had no identifiable squamous epithelium in the tissue sections examined.

All but 3 patients exhibited evidence of the inflammatory component of the podophyllin effect when the posterior lip of the cervix was examined histologically. This consisted of an accumulation of polymorphonuclear leukocytes in the cell layers of the squamous epithelium, edema, and vasodilation in the stroma. The inflammatory cell infiltrate might involve one or all layers of the epithelium as well as the subjacent stroma (Fig. 2). Vacuolization of squamous cells, often seen as a part of nonspecific inflammatory processes, was usually very extensive after one to three applications of podophyllin. At times this feature was found in all cell layers above the basal area. However, vacuolization was not prominent in the areas containing the most advanced atypia.

Mitotic figures were frequently seen in the deepest layers of the epithelium. All phases of mitosis were represented, although metaphase and anaphase figures predominated. Multipolar mitoses were not seen. Nuclear enlargement and distortion extending through the basal and intermediate layers were noted in most cervices painted one to four times.

Moderate epithelial change usually involved the deepest 3 or 4 cell layers and was noted after variable numbers of podophyllin applications, usually one to four. The nuclei were large, often paired, and at times filled the entire cell. There was considerable irregularity of the cellular outlines coarsening of the chromatin network, and prominence of the nucleoli (Fig. 3).

The most advanced atypia with a few notable exceptions was found in patients whose cervices were painted the greatest number of times. Cells were greatly pleomorphic, and nuclei were considerably distorted. The nuclear chromatin was disposed in coarse clumps. In a number of cells the nuclear membrane could not be made out (Fig. 4). These abnormalities were usually limited to the deeper one half of the epithelium but in some sections occupied almost its entire extent. No evidence of stromal invasion was found in any histologic specimen.

After many paintings the posterior lip was usually ulcerated and ragged appearing. Small, irregular sheets of abnormal epithelium were found showing considerable distortion and pleomorphism. These sheets often had little or no connection to the remaining epithelium. This was probably the source of masses of cells found in some of the cytology smears.

Atypical or premature cornification was occasionally noted in sections exhibiting all degrees of podophyllin change. Cells of this kind were found in all layers of the epithelium but most often above the basal layer. They were eosinophilic, had densely staining amorphous nuclei, and were at times found within the cytoplasm of other cells, which retained their cytoplasmic basophilia.

Whereas significant histologic effects were apparent after one to four paintings with podophyllin, the cytologic effects during this time were not spectacular, and inflammatory features predominated. The smears contained large numbers of polymorphonuclear leukocytes between and within the cells. Many cells were vacuolated and the vacuoles were often filled with inflammatory cells. There was, in addition, moderate cyto-

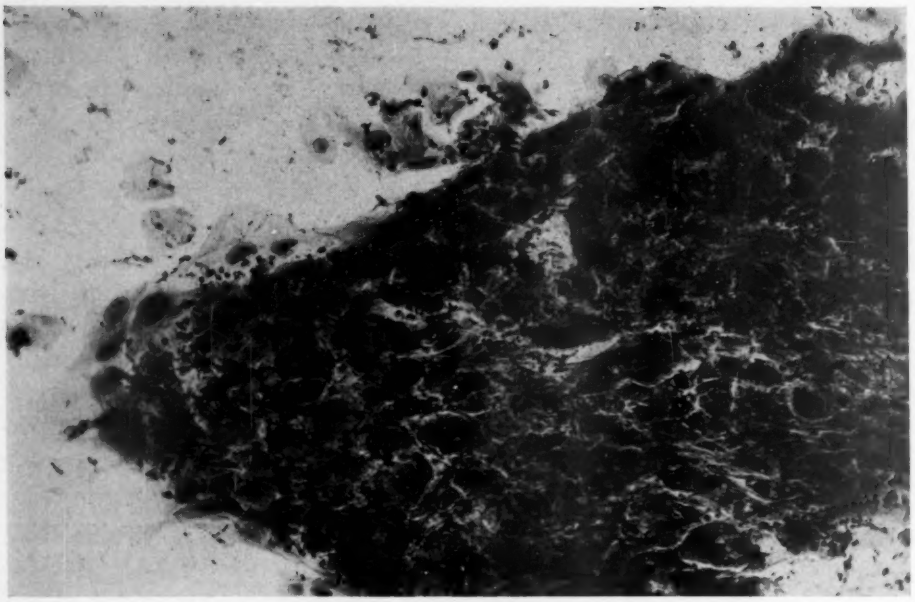

Fig. 7. A sheet of abnormal squamous cells found in a cervical smear after 14 applications of podophyllin. (×400; reduced ⅓.)

plasmic pleomorphism in these early smears. Nuclei were enlarged in some of the specimens but hyperchromatism was rare.

After 6 or more paintings, the majority of smears exhibited more advanced abnormalities. The cells appeared parabasal in type and contained large nuclei with moderate condensation of chromatin and rather prominent nucleoli (Fig. 5).

In general, the most atypical cells were recovered from patients whose cervices were painted many times. Great enlargement of the nuclei, irregularity of the nuclear outlines, clumping of the chromatin, and gross distortions of cytoplasmic outlines characterized such cells (Fig. 6). The smears of 3 patients contained sheets of grossly abnormal cells (Fig. 7). Abnormal naked nuclei were found in smears from 2 patients (Fig. 8).

Comment

Precise controls were impossible for these preliminary experiments. A single biopsy of the posterior lip of the cervix might miss a spontaneous dysplastic lesion. On the other hand, occult spontaneous dysplasia would be unusual in an appreciable percentage of 44 women.

Study of the histologic sections in sequence according to the number of podophyllin applications suggests a certain train of events. The cells in the superficial layers show the effects of inflammation. They become edematous, are infiltrated by polymorphonuclear leukocytes, and develop vacuoles. These layers which ordinarily contain cells that are dying as they approach the surface do not exhibit the nuclear effects

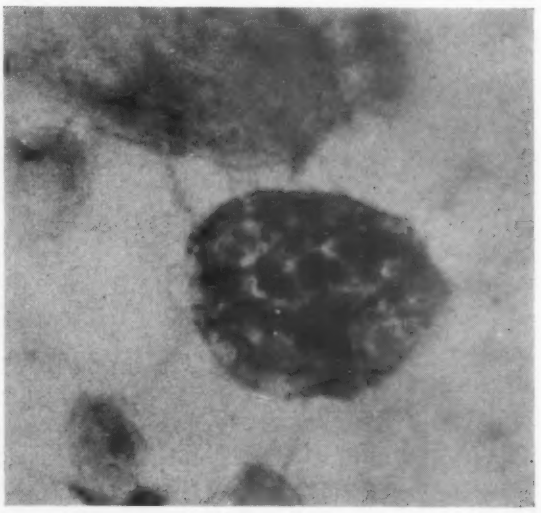

Fig. 8. Naked abnormal nucleus. Seen in a cervical smear after 10 applications of podophyllin. (×900; reduced ⅓.)

of podophyllin. These layers finally lose connection with the deeper layers of cells. Nuclear effects seem to occur in basal and parabasal layers where cells are growing and reproducing. Repeated application of podophyllin produces generation upon generation of abnormal cells which do not mature in the normal manner. Finally, a number of layers of abnormal cells are seen. However, even these cells ultimately attempt maturation. This gives a picture resembling spontaneous atypical epithelial hyperplasia. It is probable that the initial layers of cells at the surface must be removed before the altered basal cells can attain a free surface and be exfoliated. This would appear to explain the lag of cytologic atypia as compared with the histologic change.

Summary

Podophyllin produced atypia in the cervical squamous epithelia of 28 of the 44 women of this study. It produced an abnormal inflammatory response without dysplasia in 12 more women. No appreciable effect was seen in 3 women. Dysplastic lesions produced by podophyllin have many features in common with spontaneously occurring atypical epithelial hyperplasia, including the shedding of malignant appearing cells. There is at present no evidence that podophyllin is carcinogenic.

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Discussion

DR. ELIZABETH A. MCGREW, Chicago, Illinois. We must learn to distinguish between the rather common epithelial "dysplasias" of the cervix and preinvasive carcinoma; which of these morphologically similar lesions are reversible and which should be considered carcinoma in situ, capable of progressing inevitably to invasive carcinoma. Dr. Ronald Greene brought this difference to our attention some years ago by pointing out that preinvasive cervical carcinoma during pregnancy does not represent a peculiar epithelial abnormality of pregnancy and that those lesions which disappear are not preinvasive carcinoma. He did not say exactly what they were or establish criteria for differentiating them from carcinoma in situ except to illustrate them in excellent photomicrographs. People working in this field have come to recognize some relative criteria for making this distinction, such as the greater thickness of the epithelium in carcinoma in situ and the failure of the cells to mature and reorient themselves as they reach the surface. There are still many borderline lesions which are resistant to interpretation, however.

In Dr. Kaminetzky's work we have seen marked epithelial abnormality produced chemically by a noncarcinogenic substance. The cells of this epithelium looked malignant, both in smears and in sections; yet, as Dr. Kaminetzky indicated, when daily podophyllin painting of the mouse cervix is continued for several months and then discontinued, vaginal smears become normal in a few days and none of the animals develop carcinoma. He has, then, produced changes in cells which mimic malignancy, yet are temporary and reversible, thus corresponding to spontaneous cervical epithelial dysplasia. Apparently the production of these changes depends on the antimitotic action of podophyllin. It prevents the formation of the mitotic spindle so that the chromosomes cannot separate. These cells are blocked in the metaphase but survive

sufficiently to continue synthesis of nucleic acids. Their nuclei may then be reconstituted, but they have an excessive amount of nucleic acids so that they are hyperchromatic and unusually large.

Some of the carcinogenic agents also have mitotic effects; the difference is that these cause permanent mutations.

I think that this work gives us some insight into the pathogenesis of malignancy. It also adds to the battery of tools with which to study the reversible as compared with the truly neoplastic epithelial abnormalities.

Dr. S. R. Lash, Chicago, Illinois. In this experimental work carried out over a very short period the morphologic changes we have seen in cast-off cells are almost impossible to tell from those seen in carcinoma cells. The prominent nuclei, the chromatin, the marked irregularity and enlargement of the nuclei are morphologic criteria used to determine malignancy.

These were all short-term experiments. To say that this chemical is not carcinogenic is impossible in this short period of time. I think if the experiment were carried out over a long period of time such conclusions could be made. The experiments in mice will lead to conclusions on the effect in mice only.

Dr. Charles E. Galloway, Evanston, Illinois. There is another substance that produces carcinoma-like lesions in the cervix, and that is carbon dioxide snow. If carbon dioxide snow is put on the cervix, it will undergo change that looks very malignant both grossly and microscopically during the healing stage.

Dr. Kaminetzky (Closing). Dr. Lash indicated the need for long-term studies of the effect of podophyllin on human cervical epithelium. This would be very useful, but it poses a number of practical problems in finding and keeping patients on such a program. For the moment the objectives of the human studies are limited to those possible in the preoperative patient who is already hospitalized.

In response to Dr. Galloway, I have not applied carbon dioxide snow to the cervix. Tissue injury is often followed by compensatory hyperplasia. We have felt it unwise to follow the course of the podophyllin treated patient with serial biopsies for the same reason. It seemed possible that we might add another kind of tissue injury to the effect of the drug.

Acridine orange fluorochrome in the study of normal and malignant epithelium of the uterine cervix

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THE need for cytological methods that offer to cytologists a simple, short, and accurate smear technique to expedite cytological surveys and assist in identification of gynecological cancer has led to the elaboration of the acridine orange (AO) fluorescence microscopic technique, as reported by Bertalanffy and associates.[4-6]

The use of the basic fluorochrome AO NO. C.I. 788 was independently introduced by Strugger[22] and Bukatsch and Haitinger[8] in 1940 for the study of plant tissues. Schuemmelfeder[18] in 1950 applied AO to the study of normal and malignant animal and human tissues and suggested the dye-binding role of ribonucleic acid (RNA) by emphasizing that carcinoma cells in the supravital as well as in the fixed state accumulated the dye in high concentrations to produce orange and red fluorescent colors. Since his extensive investigations, numerous publications have reported upon the use of AO in human pathology as reviewed previously.[6] Van Duijn[9, 10] summarized the use of AO in microbiology and histology. Sugar and Vig[23] measured the effect of nitrogen mustard upon the AO uptake of Ehrlich ascites tumor cells. They described the alterations which occurred in the differential staining of the bright green chromatin of the nucleus, bright red nucleolus, and red cytoplasmic inclusions. Metachromatic differentiation of nuclear and cytoplasmic structures by AO was used by Kosenow[13] in hematological material stained supravitally.

The differential staining by AO of desoxyribonucleic acid (DNA) in green-yellow color and ribonucleic acid (RNA) in shades of red was reported by Schuemmelfeder,[18, 19] Bertalanffy and Bickis,[3] Armstrong[1] (acridine orange R), Armstrong and Niven[2] (acridine orange R and AO), and Breivis.[7] An explanation of the histochemical significance of the polychromatic fluorescence induced in fixed tissues stained with AO was recently offered by Schuemmelfeder, Ebschner, and Krogh,[21] and Schuemmelfeder.[20]

From the Departments of Biological Research and Pathology, Mount Sinai Hospital, and the Department of Pathology, Kaiser Foundation Hospital.

This study was supported, in part, from grants of the American Cancer Society (National Division, Grant No. T-54), The Damon Runyon Memorial Fund (DRG-416; Principal Investigator: Dr. Ludwig von Bertalanffy), American Cancer Society (California Division, Grant No. 220), and the National Institutes of Health, United States Public Health Service (Grant No. NC-FIDB CS-9624; Principal Investigator: Dr. Leo Kaplan).

The use of fluorochromes for gynecological cytological diagnosis was initiated by Friedman,[11] who used acridine yellow in combination with basic fuchsin and berberine sulfate. Mellors, Glassman, and Papanicolaou[15] applied berberine sulfate to fluorochrome nuclei of exfoliated cells of gynecological smears. Zinser[25] combined AO with primuline to stain exfoliated vaginal and cervical cells. He stated that the binding of AO fluorochrome in fixed cells occurred on the sites of the free acidic groups of RNA and DNA. He pointed out the simplicity and suitability of the method to quickly eliminate doubtful and positive smears from voluminous diagnostic material by selectively demarcating abnormal cells.

AO as a single fluorochrome for exfoliated vaginal smears was used supravitally by Fuhrman in 1955.[11a] The differential staining of the cytoplasm and nuclei by AO, buffered at different pH, was explained as a result of the varying isoelectric point of cell proteins. As maturation of the vaginal squamous epithelium is associated with a gradual decrease of cytoplasmic ribonucleoproteins, there is a shift toward neutrality in the superficial epithelial layers with a consequent change of cytoplasmic staining.

The usefulness of a single fluorochrome AO for differential staining of both nucleic acids in cytological diagnosis of exfoliated gynecological smears was reported in previous publications by Bertalanffy.[4-6]

The practical usefulness of the AO fluorescence technique in the study of exfoliated gynecological material can be summarized as follows:

1. The simple one-dye staining procedure takes 6 minutes.

2. A polychrome microscopic field is achieved, with enhancement of the visibility of colored cells on a black background.

3. The increased contrast and sensitivity of the fluorochrome technique reveals morphological details sharply.

4. The field is unobscured by red blood cells (hemoglobin quenches fluorescence).

5. Valuable cytotopochemical information aids in the identification of abnormal cells (description of normal and abnormal elements is given in previous publication).[6]

6. Screening time and fatigue of screeners are reduced.

7. Any conventional laboratory microscope with a suitable light source can be adapted and used. Detailed information concerning light sources and filters for fluorescence techniques is available.[9, 12, 14, 16, 17, 24]

The aim of this study was to establish the cytological accuracy of the AO method by comparison with the Papanicolaou technique and through confirmation by tissue diagnosis.

Materials and methods

The material for this study represented a sample of a well population. Presumably healthy women were examined, and cervical smears from the squamocolumnar junction were prepared. Materials were obtained from the Kaiser Foundation Hospital (73.9 per cent), Pacific Electric Railway Hospital Association (16.3 per cent), Mount Sinai Clinic (2.2 per cent), and private physicians (7.6 per cent). Since each individual smear represented a separate cytological situation for comparison purposes, each smear was handled as a "case." Two thousand "cases" representing smears from 1,967 patients were studied.

The smears were prepared by immediate fixation in alcohol-ether fixative and, after a minimum period of 15 minutes, were air-dried and sent to the laboratory. After fixation, smears can be kept air dried and stored in a dry place for several months without impairment of the AO staining qualities. The AO staining procedure as described previously[6] was used. Fluorochromed specimens cannot be preserved by a permanent mount. For delayed observation, smears can be stored in the refrigerator (4° C.) for several days and, after a new application of buffer, satisfactory color and morphological features are still preserved. For permanent record, photomicrographs can be taken, or the slides can be de-stained in 50 per cent alcohol and preserved in file for a stain of choice at a later date.

Table I. Cytological evaluation of cervical smears by acridine orange (AO) and Papanicolaou methods

Class	*Acridine orange diagnoses*		*Papanicolaou diagnoses*		*AO disagreements with Papanicolaou diagnosis*		
	No.	*%*	*No.*	*%*	*No.*	*Net No.*	*%*
I	1,445	72.25	1,417	70.85	+28	21	1.05
II	451	22.55	500	25.00	−49		
III	62	3.10	43	2.15	+19	19	0.95
IV	14	0.70	10	0.50	+4	3	0.15
V	11	0.55	12	0.60	−1		
Inadequate	17	0.85	18	0.90	–	–	–
Total	2,000		2,000		102 (5.10%)		

Method of evaluation

Each smear was studied after being stained with AO, de-stained, and subsequently processed by the Papanicolaou technique for re-examination. Each smear was independently studied by at least two observers with both methods. The standardized Papanicolaou Class I to V was used. The following AO classification, based upon a description of normal and abnormal elements, as reported in a previous article,[6] was used:

Class I. Negative. Absence of atypical or abnormal cells. Elements with normal fluorescence and normal morphological criteria.

Class II. Negative. Atypical cells nonmalignant.

1. Cells with abnormal cytoplasmic fluorescence (for instance, superficial squamous cells with any degree of cytoplasmic RNA or outer basal cells with increased cytoplasmic RNA content) but normal morphological criteria.

2. Cells with normal cytoplasmic fluorescence and increased nuclear fluorescence, but with normal morphological criteria.

3. Cells with normal or decreased cytoplasmic and nuclear fluorescence but morphological abnormalities of cytoplasm and nucleus.

Class III. Inconclusive. Cells very atypical but not conclusive for malignancy.

1. Cells with very abnormal cytoplasmic fluorescence greater than in Class II along with prominent nucleoli.

2. Cells with increased nuclear fluorescence. (Both groups may have abnormal morphological criteria.)

Class IV. Cells suggestive of malignancy.

1. Cells with extremely abnormal cytoplasmic fluorescence, together with morphological criteria suggestive of malignancy.

2. Cells with increased nuclear fluorescence and morphological criteria suggestive of malignancy. Attention has to be given to chromatin clumping and nucleolar prominence.

3. This group includes cells poor in cytoplasmic RNA, naked nuclei, or degenerating and necrotic cells (B type of Caspersson), but still exhibiting morphological criteria suggestive of malignancy.

Table II. Numerical differences between acridine orange and Papanicolaou classification

AO Class versus Papanicolaou Class	*No.*	*Total No.*	*Per cent of 2,000*
I vs. II	117	211	10.55
II vs. I	94		
I vs. III	7	8	0.40
III vs. I	1		
II vs. III	13	47	2.35
III vs. II	34		
III vs. IV	3	7	0.35
IV vs. III	4		
II vs. IV	1	1	0.05
III vs. V	1	1	0.05
IV vs. II	1	1	0.05
V vs. IV	1	1	0.05
Total	277		13.85

Class V. Cells conclusive for malignancy.

1. Cells with extremely abnormal cytoplasmic fluorescence and morphological criteria diagnostic of malignancy.

2. Cells with extremely increased nuclear fluorescence and morphological criteria diagnostic of malignancy. (Attention has to be given to prominence and RNA content of nucleoli as well as to chromatin clumping.)

3. This group includes cells poor in cytoplasmic RNA, naked nuclei, or degenerating B-cells, but still exhibiting morphological criteria diagnostic of malignancy.

Heavy leukocytic layers and bacteria make reading of cellular elements difficult and mask the appearance of naked hyper-or hypochromatic nuclei as well as appearance of acidophilic cells with pyknotic hyperchromatic nuclei. This applies to cells with green cytoplasm (cells poor in RNA) encountered in normal as well as in malignant smears.

To evaluate disagreements in classification by the two methods for the identical smear, the following criteria were established: "subjective differences" were those where recorded data by both methods were similar or equal and a divergent opinion of the final observer accounted for the difference; "objective differences" were those where recorded data by both methods were different and the final impression of the observer was based on these.

With the Papanicolaou diagnosis used as reference, repeat smears were requested on selected cases of Class II, and all cases of Classes III, IV, and V. Tissue biopsy was requested on selected cases of Classes II and III, and all cases of Classes IV and V. Since it is advisable that the pathologist evaluating the tissue specimens correlate them with his own Papanicolaou classification, the tissue diagnoses used were those of the senior author (L. K.).

Results

Analysis of obtained data. The distribution of ages in the smears studied showed a range from under 17 to over 80 years, with a maximum number between 20 to 69. However, 52.75 per cent were between 20 and 39 and 35.45 per cent were between 40 and 59 years of age. The expected ages of occurrences for both in situ and invasive carcinoma are included in adequate numbers.

The distribution of Classes I to V with AO and the differences from readings by the Papanicolaou method are reported in Table I. There is a noticeable shift in classification from Papanicolaou Class II to AO Class III.

Further analysis of classification differences of identical smears by both techniques is given in Table II.

Pertinent disagreements (Table III) between the two methods can be defined as those negative (Classes I and II) findings evaluated as inconclusive (Class III) or positive (Classes IV and V) by the other technique, or where positive diagnoses (Classes IV and V) are read as negative (Classes I and II) by the second technique. The pertinent differences with both Papanicolaou and AO methods occurred with 57 or 2.85 per cent of the 2,000 smears. Thirty-five were evaluated as AO Class III and 34 as Papanicolaou Class II. Fourteen smears were read as AO Class II, 13 as Papanicolaou Class III, and one as Papanicolaou Class IV. Seven smears classified as AO Class I were read as Papanicolaou Class III. There was one pertinent difference with AO Class IV and none with AO Class V. Relating the pertinent differences to the total number of each AO class showed that they occurred in 0.48 per cent of Class I (7 of 1,445 smears), 3.10 per cent of Class II (14 of 451), 56.45 per cent of Class III (35 of 62), 7.14 per cent of Class IV (1 of 14), and in none of those smears read as AO Class V (Tables I and III).

The findings when the disagreements encountered by the classification of identical smears with both methods on the basis of "subjective" and "objective" differences were evaluated are given in Table IV. The AO technique showed more morphological and cytochemical data about atypical cells. Therefore, more identical smears were evaluated as AO Class II versus Papanicolaou Class

Table III. Cytological evaluation of cervical smears by acridine orange (AO) and Papanicolaou methods—pertinent differences

Comparison							*Comparison*						
Acridine orange		*Papanicolaou Class*					*Papanicolaou*		*Acridine orange Class*				
Class	*No.*	*I*	*II*	*III*	*IV*	*V*	*Class*	*No.*	*I*	*II*	*III*	*IV*	*V*
I	7	–	–	7	–	–	I	1	–	–	1	–	–
II	14	–	–	13	1	–	II	35	–	–	34	1	1
III	35	1	34	–	–	–	III	20	7	13	–	–	–
IV	1	–	1	–	–	–	IV	1	–	1	–	–	–
V	–	–	–	–	–	–	V	–	–	–	–	–	–
Total	57 (2.85%)						Total	57 (2.85%)					

Table IV. Classification of disagreements AO versus Papanicolaou in 2,000 cases based upon subjective and objective differences*

Class		*Total cases*		*Subjective differences*		*Objective differences*	
AO	*Papanicolaou*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	II	117	5.85	57	2.85	60	3.00
I	III	7	0.35	4	0.20	3	0.15
II	I	94	4.70	27	1.35	67	3.35
II	III	13	0.65	9	0.45	4	0.20
II	IV	1	0.05	1	0.05	0	0.00
III	I	1	0.05	1	0.05	0	0.00
III	II	34	1.70	12	0.60	22	1.10
III	IV	3	0.15	3	0.15	0	0.00
III	V	1	0.05	1	0.05	0	0.00
IV	II	1	0.05	1	0.05	0	0.00
IV	III	4	0.20	2	0.10	2	0.10
V	IV	1	0.05	0	0.00	1	0.05
Total		277	13.85	118	5.90	159	7.95

*"Subjective differences": recorded data by both methods were similar or equal and a divergent opinion of the final observer accounted for the difference; "Objective differences": recorded data by both methods were different and final opinion of observer was based on these.

I and AO Class III versus Papanicolaou Class II because of the preponderance of objective differences. Group AO III will merit close observation and repetitive follow-up studies over a long period of time, as it may represent the group of potential malignancies. In the higher Classes IV and V, the minor differences encountered cannot be evaluated, as the total number of cases was very small. Generally, analysis of individual cases showed that ample data were recorded by both methods and that classification of smears in Class IV and Class V matched closely.

Follow-up information. It was more difficult to obtain follow-up information on cases with Class II and III than in cases with Class IV and V smears. Repeat smears and biopsies were requested on basis of the Papanicolaou diagnosis. Thirty-six (1.8 per cent of the 2,000 cases) biopsies were requested and 33 (1.65 per cent) were received. These included 5 nonneoplastic endometrial curettements, without simultaneous cervical biopsies. Therefore, 28 patients only were used for correlation study (30 biopsies).

Anatomic findings in surgical specimens. A biopsy was considered to be "inadequate" when it was fragmentary or consisted of punch biopsies that represented less than the total mucosal surface of the external os or endocervical canal, and/or did not include adequate representation of the squamocolumnar junction. This decision automatically declared that the properly per-

formed cone biopsy and/or total hysterectomy was considered to be an "adequate" sampling of this anatomic region. In each of the 28 patients from whom cervical biopsy specimens were obtained, the slides were reviewed and the morphological evaluation was made by the reviewer surveying the cytological smears on the same patient. In each instance, the original blocks were obtained and numerous serial sections were prepared. The value of the latter procedure cannot be minimized when the location of minute lesions or additional features of cervical lesions are sought.

Eighteen of the 28 patients were considered to have had "inadequate" (small-tiny) punch biopsies. Nine were studied by means of a cone biopsy (2 followed by hysterectomy), and 3 by means of hysterectomy specimens (one without prior biopsy) (Table V). In 88 per cent (8 of the 9) of patients studied by the cone biopsy method, a positive neoplastic diagnosis could be clearly established or considered. In 7 of these 8, a forthright diagnosis of carcinoma could be made, and in one instance the distinction between an atypical metaplasia and squamous cell carcinoma in situ could not be firmly established. In contrast, in 33 per cent (6 of the 18) of patients studied by punch biopsy a positive neoplastic diagnosis could be established or considered (Table V). One of these 6 patients appeared to have an infiltrating and 5 appeared to have an in situ squamous cell carcinoma. This difference in biopsy yield, in a group of patients with similar abnormalities encountered in smears, studied by means of AO and Papanicolaou methods, does appear to indicate the inadequacy of the punch biopsy diagnostic method. This is perhaps further emphasized by the fact that of the 12 patients with "inadequate" nonneoplastic (small-tiny) biopsy findings, there were 2

Table V. Nature of surgical specimen

Type	*Total No.*	*Biopsy*				*Smears taken after negative biopsy*		
		Adequate		*Neoplasms or possible neoplasms*		*No. taken*	*Inconclusive or positive*	
		No.	*%*	*No.*	*%*		*No.*	*%*
Cone biopsy (2 followed by hysterectomy*)	9	9	100	8	88	0	0	–
Small-tiny punch biopsy	18	0	0	6	33	2	2	100
Hysterectomy with/without prior biopsy*	3	3	100	3	100	0	0	–
Total specimens	30	12	40	17	56	2	2	100

*Two hysterectomies were preceded by cone biopsy.

Table VI. Diagnoses encountered

Neoplasms	*No.*	*Adequate biopsy*		*Incidence*		*Inconclusive or positive smears after negative biopsy*	
		No.	*%*	*% of 1,967 patients*	*% of 14 positive biopsies*	*No.*	*%*
Squamous cell carcinoma							
In situ	11	6	55	0.55	78	–	–
Invasive	2	1	50	0.10	14	–	–
Adenocarcinoma, uterus	1	1	100	0.05	7	–	–
Possible squamous cell carcinoma in situ	1	0	0	0.05	–	–	–
Indecisive atypical metaplasia	1	0	0	0.05	–	1	100
Negative biopsy	12	1	8	–	–	1	16
Total patients	28	9	32	–	–		

Table VII. Morphological evaluation of surgical specimens and related cytological findings

	No.	*Papanicolaou*				*Acridine orange (AO)*			
		II	*III*	*IV*	*V*	*II*	*III*	*IV*	*V*
1. All biopsies									
Neoplasms									
Carcinoma of cervix	13	–	2	1	10	1	1	1	10
Carcinoma of endometrium	1	–	1	–	–	–	1	–	–
Inconclusive diagnoses									
Possible carcinoma of cervix	1	–	1	–	–	–	1	–	–
Indecisive atypism	1	–	–	1	–	–	1	–	–
Nonneoplastic biopsy	12	1	7	2	2	2	5	4	1
Total	28	1	11	4	12	3	9	5	11
2. Adequate biopsies only									
Carcinoma of cervix	7	–	1	–	6	–	1	–	6
Carcinoma of endometrial	1	–	1	–	–	–	1	–	–
Possible carcinoma of cervix	1	–	1	–	–	–	1	–	–
Indecisive atypism	–	–	–	–	–	–	–	–	–
Nonneoplastic biopsy	1	–	–	1	–	–	–	–	1
Total	10	0	3	1	6	0	3	0	7

who continued to have either inconclusive or positive smears subsequent to the nonneoplastic biopsy (Table V). In the remaining 10 of the 12 patients with "inadequate" nonneoplastic biopsy finding, no follow-up smears and no additional biopsy specimens have as yet been obtained.

Of 28 patients studied by biopsy of the cervix, 12 yielded nonneoplastic tissues, one showed the presence of an indecisive type of atypical metaplasia, one showed changes wherein the distinction of a squamous cell carcinoma in situ from a markedly atypical metaplasia could not be made, one showed the presence of an endometrial adenocarcinoma, 2 were found to have infiltrating squamous cell carcinomas, and, in 11 patients, a squamous cell carcinoma in situ could be identified (Table VI). Of the 1,967 patients studied by cervical smears, there were, therefore, 13 with cervical and one with endometrial carcinomas demonstrated anatomically. This represents an incidence of 0.7 per cent malignancy rate for the group of 2,000 smears. An analysis of these neoplasias shows the incidence for squamous cell carcinoma in situ to be 0.55 per cent, for infiltrating squamous cell carcinoma to be 0.1 per cent, and for endometrial adenocarcinoma, 0.05 per cent for this group of apparently well women (Table VI).

Correlation of morphological biopsy abnormalities with both AO and Papanicolaou cervical smear findings in these patients was obtained (Table VII). With the Papanicolaou method there were 12 smears evaluated as Class V, 4 as Class IV, 11 as Class III, and one as Class II; by the AO method there were 11 smears evaluated as Class V, 5 as Class IV, 9 as Class III, and 3 as Class II (Table VII). A review of the charts of patients with Class II smear findings yields the following information: One read as AO Class II and Papanicolaou III was that of a 59-year-old symptomless woman, from whom two successive punch biopsy specimens of the cervix were obtained, both of which were evaluated as showing cystic endocervical polyp, chronic cystic endocervicitis, and benign squamous cell metaplasia. The second, read as AO Class II, Papanicolaou III, was that of a 55-year-old woman who had had punch biopsy studies of the cervix following the smear study. This showed merely chronic cervicitis and tiny foci of squamous cell metaplasia. The third, read as AO II and Papanicolaou IV, was

that of a 31-year-old pregnant woman with clinical cervicitis and showed by punch biopsy an extensive squamous cell carcinoma in situ of the cervix with foci of infiltration of the underlying submucosa. An ex post facto rereading of the smears confirmed the original evaluation of the Papanicolaou findings. A review of the notes made at the time of the first study by the AO technique revealed some variations in nuclear size and degree of nuclear hyperchromasia in inner and outer basal cells as well as in intermediate cells. These findings were considered to be insufficient for a Class AO III diagnosis. A second smear from the cervix of this patient was obtained, subsequent to the completion of the first 2,000 smears (3 months later) and was evaluated as AO Class IV and Papanicolaou Class V. The latter smear was obtained on the day and at the time the punch biopsy specimens of the cervix were secured, with findings as noted above. The one instance of Papanicolaou Class II read as AO Class III occurred in a 27-year-old woman, 6 weeks post partum, at the time of cervical smear study. Tiny punch biopsies showed merely chronic cervicitis, glandular hyperplasia, and benign squamous cell metaplasia.

The one instance wherein a nonneoplastic, adequate biopsy was associated with a cervical smear containing cells classified as Papanicolaou IV and AO V (Table VII), can be explained. This patient was a 51-year-old symptomless woman studied by cervical smears on May 15, 1958, with the above findings, and again on June 3, 1958. On June 10 a cone biopsy showed that the mucosa of the exocervix and endocervical canal were denuded of all epithelium. In its place was found an extensively inflamed granulation tissue showing surface necrosis. The cervix had received no specific therapy prior to the biopsy. One must presume that the area from which the abnormal cells were obtained in the smears had been effectively removed in the process of obtaining the smears. This conclusion was reached after serial sections were prepared from the single block containing all of the removed tissue.

Table VIII. Cytology accuracy of both techniques as confirmed by tissue diagnosis in 2,000 smears (1,967 patients)

False-negative smears*	
Papanicolaou	
No. of cases of false-negative smears (Papanicolaou negative–biopsy positive)	0 (0.00%)
Acridine orange	
No. of cases of false-negative smears (AO negative–biopsy positive)	1 (0.05%)
(Note: repeat smear 3 months later from this case = Papanicolaou Class V and AO Class IV)	
False-positive smears†	
Papanicolaou	
No. of cases of false-positive smears (Papanicolaou positive–biopsy negative)	4 (0.20%)
(Note: 3 cases had "inadequate biopsy" specimens and 1 cone biopsy exhibited completely denuded, nonepithelium bearing necrotic, inflamed mucosal surface)	
Acridine orange	
No. of cases of false-positive smears (AO positive–biopsy negative)	5 (0.25%)
(Note: 4 cases had "inadequate biopsy" specimens and in 1 of these cases a follow-up cervical smear still shows a Papanicolaou Class III pattern; 1 cone biopsy exhibited completely denuded, nonepithelium bearing necrotic, inflamed mucosal surface)	

*False-negative smears = Classes I and II.
†False-positive smears = Classes IV and V.

Cytological accuracy of AO technique. Our experience with false-negative and false-positive smears in these first 2,000 smears (1,967 patients) studied (Table VIII) compares very favorably with the data in the literature. The cytological accuracy of AO and Papanicolaou techniques is determined in Table VIII by confirmation with the corresponding tissue diagnoses. There was no false-negative smear with the Papanicolaou method and one (0.05 per cent) with the AO method for 2,000 cases (1,967 patients).

False-positive smears were 4 (0.20 per cent) with the Papanicolaou method and 5 (0.25 per cent) with the AO method for the same number of cases. The adequacy of the tissue specimens in the series of false-positives is discussed in Table VIII.

A false-negative smear was defined as a Class I or II (cytologically negative) smear with a biopsy specimen which contained neoplasm. There were no false-negative smears encountered by the Papanicolaou technique. There was one false-negative smear encountered by the AO method (Table VIII). This patient, as noted above, had a repeat cervical smear evaluation 3 months later as Papanicolaou Class V and AO Class IV. The degenerating malignant cells in the original smear exhibited no sharp diagnostic criteria by the AO technique. A false-positive smear consisted of a Class IV or V smear with a nonneoplastic cervical biopsy. With the Papanicolaou technique, there were 4 false-positive smears (Table VIII). Three of these patients had "inadequate" biopsy specimens submitted, and the fourth patient had a cone biopsy, as noted above, where the tissue findings showed a nonepithelium-covered, necrotic, inflamed mucosal surface. This latter patient, in a strict sense, ought to have been categorized as having an "inadequate" biopsy, since no opportunity was or will be forthcoming to demonstrate the source of the abnormal cells encountered. One of the 3 patients with "false-positive" smears and "inadequate" biopsy showed a denuded chronically inflamed, cervical mucosal surface.

There were 5 patients with false-positive smears encountered by the AO method (Table VIII). Four of these had "inadequate" biopsy specimens submitted, and one patient (see false–Papanicolaou-positive smear), studied by cone biopsy, exhibited a nonepithelium-covered, necrotic, inflamed, mucosal surface. In addition, the biopsy specimen from one patient did not include proper representation of the squamocolumnar junction, and another showed no squamocolumnar junction at all. Still another (see false–Papanicolaou-positive smear) showed a partly denuded, chronically inflamed, ulcerated mucosal surface. Of great significance is the fact that one of these continued to show a Papanicolaou Class III cervical smear one month after the "inadequate" biopsy. In 2 of these AO false-positive smears, the "inadequate" biopsy was preceded surgically by a diagnostic dilatation and curettage of the endometrial mucosa. The latter strippings showed no neoplasm. It must be emphasized, however, that such procedures regularly denude cervical surfaces and obscure cervical anatomy, defeating attempts at morphological evaluation of epithelial abnormalities and identification of the source of the bizarre cytology findings in the preceding cervical smears.

Comment

The differences encountered by both techniques (AO and Papanicolaou) in this study were evaluated according to "subjective" and "objective" criteria, in order to establish the value of cytotopochemical (RNA and DNA) information as an additive to morphological observations. The validity of these data was obtained by the ultimate clinical course of the patient and morphological findings in tissue specimens. Variations in individual cell collection and biopsy technique (approximately 20 gynecologists participated in this study) probably account for the occasional inadequate representation of abnormal cells in smears and the resulting minor discrepancies with tissue diagnoses.

Factors influencing the RNA content of the cervical epithelium, such as age of patient, normal and abnormal menstrual cycles, endocrine abnormalities, and therapeutic states are the subject of a separate study.

In addition, there are numerous factors influencing the adequacy of cytology and tissue specimens and their evaluation. However, in this study, a remarkable uniformity and reliability was achieved by both cytological methods (AO and Papanicolaou) when related to morphological findings in tissue specimens.

The AO method has been found to be an

accurate, short, diagnostic smear technique suitable for gynecological cytology. The added cytotopochemical information (RNA and DNA) assists in sharply identifying abnormal cells and offering more descriptive data for atypical cells than the Papanicolaou technique. This is especially true for cells of Classes II and III. It is hoped that the AO technique may improve the diagnostic criteria for the critical Class III. Long-range observations of a large number of patients of this type will be necessary to follow changes in such abnormal epithelial cells and establish the significance of increased cytoplasmic and nucleolar basophilia (RNA) for detection of early malignancy.

Summary

In a study of 2,000 consecutive smears (1,967 apparently well women), 0.7 per cent of "positive" cytological findings by each method (AO and Papanicolaou) were confirmed by tissue diagnoses. The cytological accuracy of the AO method was established by comparison with the Papanicolaou method and tissue diagnoses. The value of additional cytotopochemical criteria (RNA and DNA) for identification of abnormal cells was confirmed.

Diagnostic criteria for the AO classification were defined. More morphological and cytochemical details were encountered in cells classified as AO Class II (Papanicolaou Class I) on identical smears. A larger group of AO Class III (Papanicolaou Class II) was encountered. Cytological diagnoses by both methods in Classes IV and V were almost identical and recorded data by both techniques correlated well.

Conclusion

The aim of this study was to test the cytological accuracy of the AO method by comparison with the Papanicolaou technique and through confirmation by tissue diagnosis in order to establish the AO technique as a convenient diagnostic method for exfoliated gynecological smears.

Both aims were fulfilled satisfactorily, and the data obtained compare favorably with the postulated criteria for accuracy of a cytological method.

We wish to express our appreciation to E. Craig Heringman, M.D., and Harold H. Boros, M.D., of the Pacific Railway Association Hospital and Jack Gordon, M.D., of the Kaiser Foundation Hospital, as well as to the contributing gynecologists of these hospitals and the Mount Sinai Hospital and Clinic. We also wish to thank Mrs. Joan Maudlin and Mrs. Lily Peterman for their technical assistance and Mrs. Ruth Atlas for preparation of the manuscript.

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Protein characterization in normal and abnormal cervical squamous mucosa—"pH signature"

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IN FURTHERING our understanding of neoplasia, advances in chemical delineation of normal and cancer cells are necessary, in addition to the classical studies of the morphology of the cells. New techniques developed by histochemists and cytophysicists have been employed in our laboratory for some years.

A technique with some potential is that of "pH signature."[11] For some years it has been recognized that the variable which affects dyeing most profoundly is that of pH. Staining in an alkaline medium favors the uptake of basic dye, and staining in an acid medium favors the uptake of acid dye. This was recognized in tissue staining and was employed on an empirical basis. With the demonstration of the amphoteric nature of proteins, interest was revived in this technique. Histochemical characterization by pH control is not new. Singer[11] has reviewed the history of this approach.

Proteins contain both acidic and basic groups which by their dissociation give rise, respectively, to positive and negative charges on protein molecules. Proteins differ according to the nature and number of their constituent amino acids and conjugated substances. The over-all positive or negative charge depends on the relative number of basic or acidic side groups. The ability of a protein to take up acidic or basic dye according to the acidity of the environment is an expression of the amphoteric properties and the charge on the dye ion. Uptake of dye in a range of pH follows closely alteration in electric charge on the protein.[11]

In this study, we have employed a basic dye (methylene blue) and an acidic dye (light green) in a range of pH to stain various types of cervical epithelium. Although the method did not allow specific differentiation between cancer and normal epithelium, some interesting observations were made.

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Presented at the meeting of the Inter-Society Cytology Council, Detroit, Michigan, Nov. 21, 1959.

This investigation was supported by research grants from the National Cancer Institute (C-2719), National Institutes of Health, United States Public Health Service, and the Damon Runyon Memorial Fund (DRG-352).

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Materials and methods

Sixteen cases of metaplasia, 18 cases of atypical hyperplasia, 17 cases of carcinoma in situ, and 15 cases of invasive squamous cell carcinoma were studied. These cases were selected from the files of the Institute of Pathology of Western Reserve University, and of the University Hospitals of Cleveland. All of the diagnoses were made by Dr. James E. Reagan of Western Reserve University according to published criteria.[8, 9] Only cases in which there were normal exocervical mucosa and the characteristic

abnormal epithelium in the same slide, in amounts sufficient to permit study, were utilized. This same material had been previously employed in interferometric studies.[6]

Cases of each entity were studied in rotation so that a gradual and undetected change in evaluation could not simulate differences in findings among the types of cases.

Sections 3 μ in thickness were cut from the paraffin blocks. They were stained with 5×10^{-4} M solutions of methylene blue (Harleco) or of light green (S.F. color index No. 670, Harleco) according to the method of Dempsey and Singer[3] as modified by Barrnett.[1] Methylene blue was employed at pH 3,4,5,6,7,8. Light green was employed at pH 3,4,5,6. Slides were stained overnight, dehydrated in alcohol and xylol, and mounted in H.S.R. mounting medium (Harleco).

Each section was examined and the staining characteristics of various cell structures evaluated on a subjective scale varying from 0 to 6. Generally the most intensely staining object with methylene blue at pH 8 was rated as 6, and everything else compared in general intensity of stain. Since the light green did not stain any individual structure as intensely as maximum methylene blue staining, rating of the light green staining was in general lower.

Results

1. Basal nuclei. No differences were noted between categories with either light green or methylene blue stain. There was no difference between the cells of the normal epithelium and the cells of the abnormal epithelium as regards staining intensity (Fig. 1, *a, b* and Fig. 2, *a, b*).

2. Basal cell cytoplasm. No differences between categories or between normal and abnormal cells were seen in either methylene blue or light green staining (Fig. 1, *c, d* and Fig. 2, *c, d*).

3. Middle nuclei. With methylene blue stain, the middle nuclei of carcinoma in situ, atypical hyperplasia, and carcinoma, in that approximate order, stained darker; they retained their affinity for basic dye even in a relatively acid medium (Fig. 1, *f*). All except metaplasia were darker than the normal epithelium in the same section (Fig. 1, *f*). The same findings hold true with light green stain, but the staining was less intense and so the difference was less remarkable (Fig. 2, *e, f*). It was apparent that middle nuclei did not stain as intensely as did the basal nuclei in normal epithelium (Fig. 1 *a, e*). There was much less difference in intensity of staining between the basal and middle nuclei of abnormal epithelium (Fig. 1, *b, f*). With methylene blue, the abnormal middle nuclei of carcinoma in situ were darker than these nuclei of the other three categories. This was the only instance in this study where there was notable difference between carcinoma in situ, atypical hyperplasia, and invasive carcinoma (Fig. 1, *f*).

4. Middle cytoplasm. With methylene blue, all categories stained more intensely in abnormal epithelium than in normal epithelium (Fig. 1, *g, h*). The same held true with light green but to a lesser degree (Fig. 2, *g, h*). The cytoplasm of the middle cells of cases of metaplasia stained less intensely with methylene blue than they did in the other three categories of abnormal epithelium (Fig. 1, *h*).

5. Superficial nuclei. With both methylene blue and light green, the superficial nuclei of atypical hyperplasia, carcinoma in situ, and carcinoma were stained more intensely than was metaplasia (Fig. 1 and Fig. 2, *j*). Except for metaplasia, the abnormal epithelium was stained more intensely than was the normal epithelium (Fig. 1 and Fig. 2, *i, j*). In normal epithelium there was no variation between categories (Fig. 1 and Fig. 2, *e, f, i, j*).

6. Superficial cytoplasm. The cytoplasm of the abnormal epithelium stained more intensely than the cytoplasm of the normal epithelium (Figs. 1 and 2, *k, l*). In the abnormal areas, the cytoplasm of this layer stained less intensely in cases of metaplasia than in the other three categories, which could not be differentiated by staining intensity (Fig. 1 and Fig. 2, *l*).

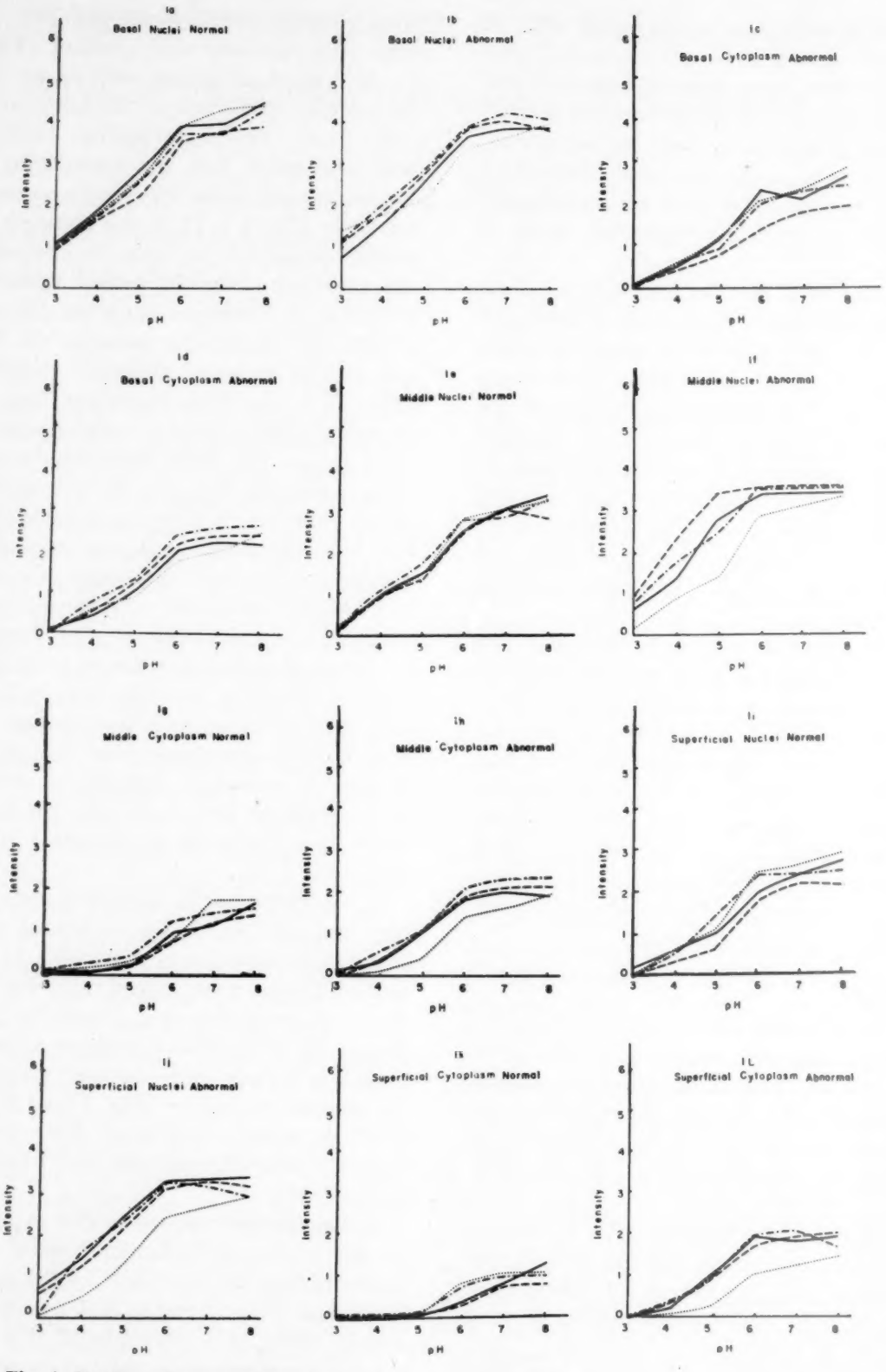

Fig. 1. For legend see opposite page.

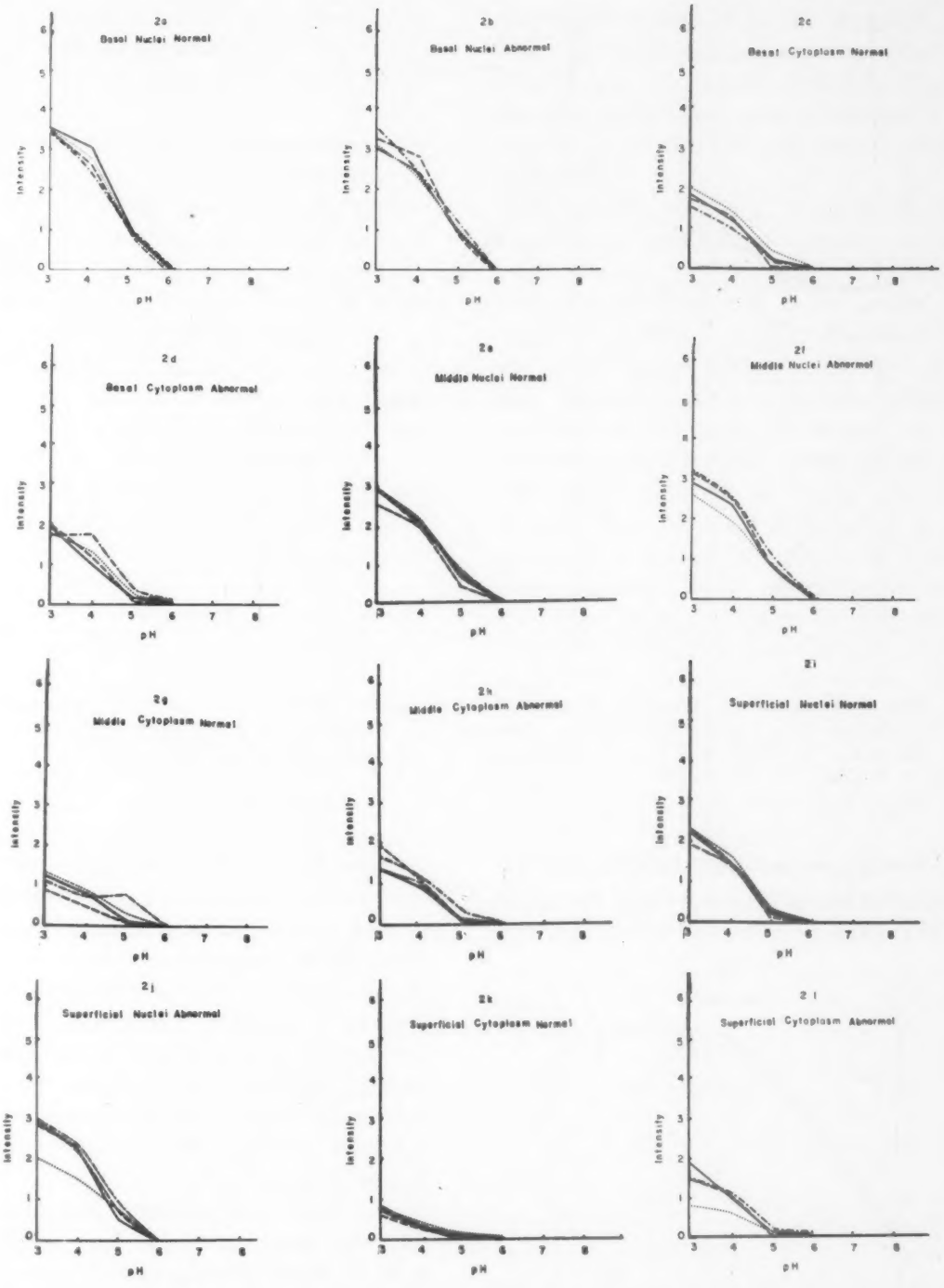

Fig. 1. Diagrams of intensity of methylene blue staining in relation to pH of various cellular components in normal and abnormal squamous epithelium from cases of metaplasia, atypical hyperplasia, carcinoma in situ, and invasive carcinoma of the cervix: *a*, normal basal nuclei; *b*, abnormal basal nuclei; *c*, normal basal cytoplasm; *d*, abnormal basal cytoplasm; *e*, normal middle nuclei; *f*, abnormal middle nuclei; *g*, normal middle cytoplasm; *h*, abnormal middle cytoplasm; *i*, normal superficial nuclei; *j*, abnormal superficial nuclei; *k*, normal superficial cytoplasm; *l*, abnormal superficial cytoplasm. (Case type code similar in all figures: carcinoma ————, carcinoma in situ – – – – –, atypical hyperplasia —.—.—.—, metaplasia . . . . .)

Fig. 2. Diagrams of intensity of light green staining in relation to pH of various cellular components in normal and abnormal squamous epithelium from cases as noted in Fig. 1, using same letter designation. (Case type code similar to that of Fig. 1.)

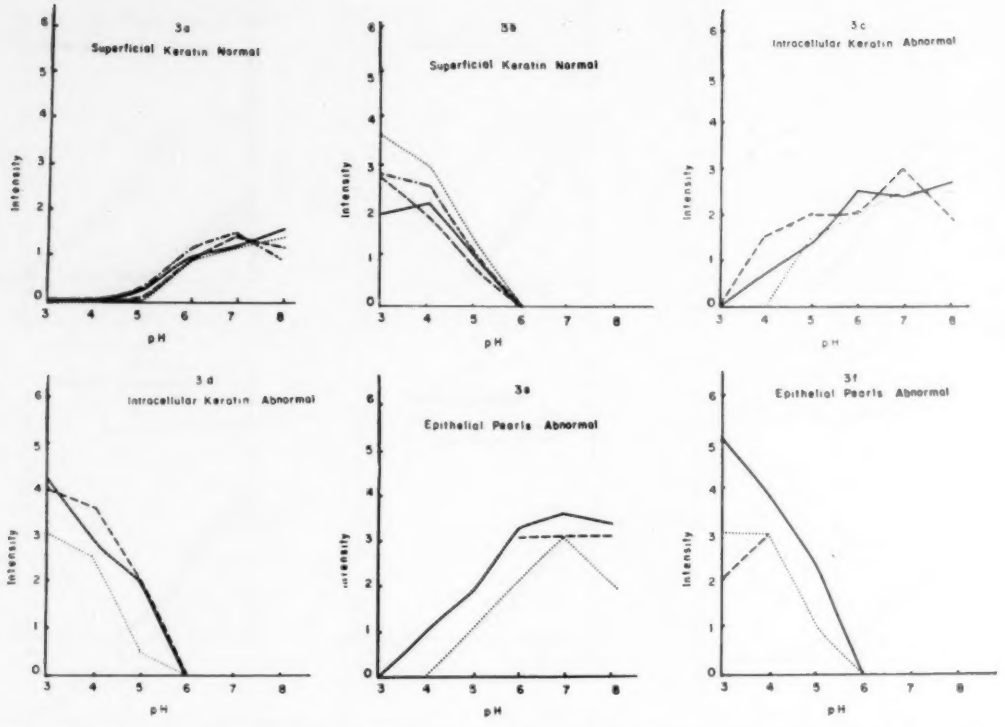

Fig. 3. Diagrams of intensity of staining of superficial keratin (*a*, normal; *b*, abnormal; methylene blue), intracellular keratin abnormal; (*c*, methylene blue; *d*, light green), epithelial pearls; (*e*, methylene blue; *f*, light green) in cases and types as indicated in Fig. 1.

7. Keratin, intracellular keratin, and epithelial pearls. Superficial keratin was present in 9 cases of metaplasia, 10 of atypical hyperplasia, 10 of carcinoma in situ, and 5 of invasive carcinoma. This keratin was studied over the normal areas in these cases. Intracellular keratin was noted in 2 cases of metaplasia, 1 case of carcinoma in situ, and in 4 cases of carcinoma. Epithelial pearls were seen in 1 case of metaplasia, 1 case of carcinoma in situ, and 4 cases of carcinoma. Such a small number of cases rendered drawing of conclusions unwise. Epithelial pearls and intracellular keratin stained with equal intensity, and with more intensity than superficial keratin (Fig. 3, *a* to *f*). Light green stained the intracellular and superficial keratin more intensely than did methylene blue (Fig. 3, *a* to *d*). This was the reverse of most of the components of cervical epithelium.

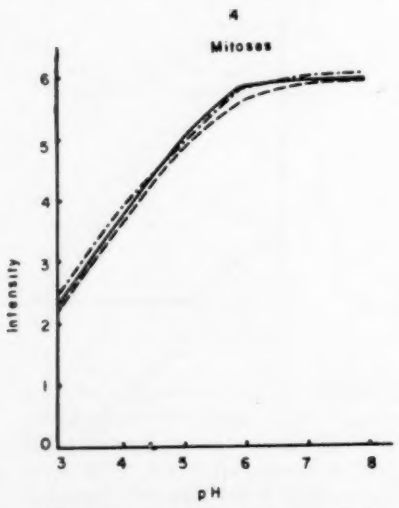

Fig. 4. Diagrams of intensity of staining of mitoses from abnormal epithelium in cases of metaplasia, atypical hyperplasia, carcinoma in situ, and invasive carcinoma of the uterine cervix (methylene blue). (Case type code similar to that of Fig. 1.)

Epithelial pearls were the most intensely stained structures of all with light green (Fig. 6). The loss of affinity for this acid stain was quite rapid though, with decreasing acidity. Interestingly, the epithelial

pearls of cancer stained more intensely in strongly acid solution than did the pearls found in the 2 cases other than cancer (Fig. 3, *f*).

8. **Mitoses.** Almost no mitoses were seen with the light green stain. With methylene blue they were the most intensely stained structure of all (Fig. 4). They retained their affinity for basic dye even in relatively acid medium (Fig. 7, *a, b*). Very few mitoses were seen in normal epithelium.

9. **Nucleoli.** No differences were noted between the nucleoli of normal and abnormal epithelium regarding intensity of stain. In methylene blue they stained very intensely in alkaline medium but the intensity of staining fell off rapidly in acid medium. The reverse held true for light green stain (Fig. 5, *a, b*). Except for mitoses, the nucleoli were the most intensely stained object with methylene blue.

Comment

Proteins are undoubtedly the only cell constituents contributing materially to this study. Lipids and carbohydrates were leached out by the solvents involved in tissue preparation.

In solution, the acidic and basic groups of proteins dissociate, giving rise to positive and negative charges on the molecule. The basic and acidic groups comprise the free side groups of certain amino acids, the terminal amino and carboxyl groups of the protein molecule, and conjugated charged substances.

Lysine, histidine, and arginine are basic amino acids because they contain free basic side groups ($NH3^+$). Aspartic, glutamic, and B-hydroxyglutamic acids possess free carboxyl (COO^-) groups, therefore they are acidic amino acids. In addition, serine and tyrosine possess hydroxyl radical in addition to the carboxyl group, so they are also acidic. Of course, many amino acids have equal numbers of basic and acidic groups; they have no dissociating groups except those which are used in the peptide linkages; hence, they are not available to contribute any net charge to the protein molecule. From the sum of positive and negative charges contributed to the protein by these amino acids, the acidity or alkalinity of the protein is determined.[11]

The "pH signature" technique has not revealed any sharply differentiating feature between cancer and normal tissue. There is no marked difference between normal and abnormal epithelium as regards their ability to bind a basic or acidic dye. On the other

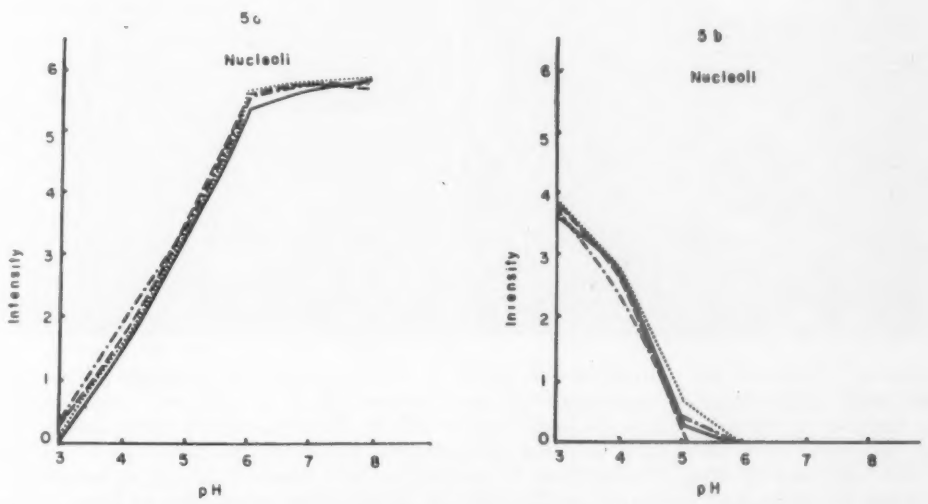

Fig. 5. Diagrams of intensity of staining of nucleoli from cases of metaplasia, atypical hyperplasia, carcinoma in situ, and invasive carcinoma of the uterine cervix: *a*, methylene blue; *b*, light green. (Case type code similar to that of Fig. 1.)

hand, all of our findings lend credence to the belief that metaplastic epithelium has little intrinsic difference from normal epithelium. Atypical hyperplasia, however, was very similar to carcinoma in situ and invasive carcinoma when studied by this method. The already well-known hyperchromatism of these three categories is verified. The intensity of staining of superficial and middle cells is increased in atypical hyperplasia, carcinoma in situ, and invasive carcinoma. Cytoplasmic basophilia is confirmed. This study lends support to the concept that atypical hyperplasia represents a stage of, if not the same basic process as, carcinoma in situ.

Observation of the keratin staining has been interesting. The only consistent chemical difference between the composition of keratins and of cell proteins is the higher cystine content of keratins. It is associated with a decrease in amino acids containing sulfhydryl. The probable mechanism is the formation of a disulfide cross linkage by the closure of amino acids containing sulfhydryl in neighboring polypeptide chains.[10]

The affinity of mitotic figures for basic dye, even in relatively acid medium, is very interesting. This may be due to nucleic acid concentration within the mitotic figures. Nucleoproteins are formed by a combination of nucleic acids and proteins. They are

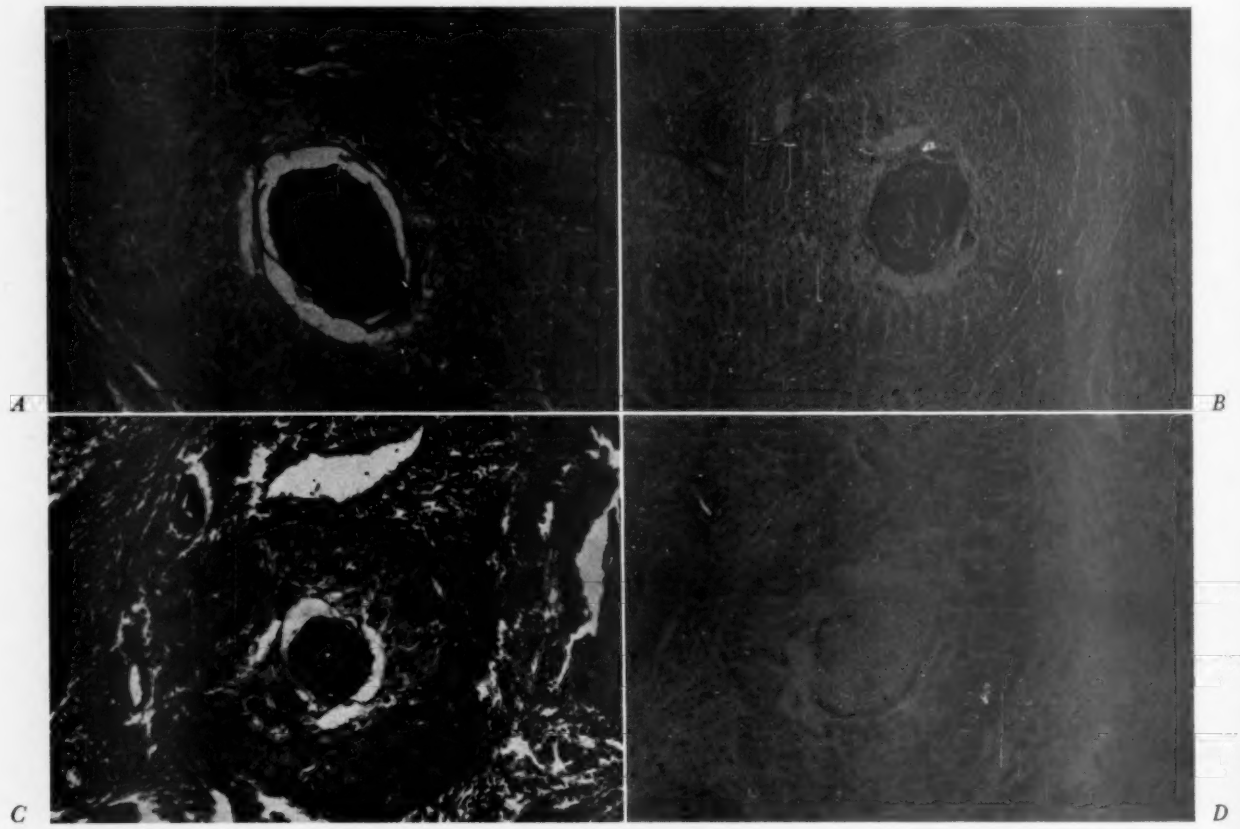

Fig. 6. Invasive squamous cell carcinoma of cervix (×132; reduced ⅓). *A,* Light green, pH 3. Note heavy staining of epithelial pearl, comparatively poor nuclear detail of adjacent viable carcinoma cells, and heavy staining of fibrous stroma. *B,* Light green, pH 5. The keratinized pearl retains considerable affinity for the stain, with other structures less well stained. *C,* Methylene blue, pH 8. Intense staining of nuclei and moderate staining of cytoplasm of carcinoma cells. Marked affinity of keratin in epithelial pearl for stain. *D,* Methylene blue, pH 4. The keratin pearl shows essentially no stain. This is not a constant finding from case to case, since in some instances surface keratin and epithelial pearls had considerable affinity for methylene blue at comparatively low pH. The nuclear elements, especially a few mitotic figures, retain considerable affinity for methylene blue.

basophilic because of the presence of free phosphate groups. DNA is probably the most important building stone in all cells. With some exceptions there is remarkable constancy in DNA content in diploid, somatic, nondividing nuclei. On the other hand, Leuchtenberger and asociates[7] found that the interphase nuclei from precancerous and malignant tissues carry higher amounts of DNA and more scatter is shown from cell to cell than is found in normal homologous tissue. Bielecki[2] showed DNA content to be higher in cervical carcinoma, carcinoma in situ, and cervical paratypia. This may be explained by growth and mitotic activity. DNA is synthesized in a relatively short period of time. The stage at which DNA doubling occurs in the mitotic cycle is open to discussion, but is often completed in interphase. The stage in which it is synthesized may vary from one tissue to another.

Some error is inherent in a subjective study such as this. Careful evaluation of types of cases in rotation has minimized this, when the mean values of all cases are compared. Photometric methods of evaluation of staining intensity would have had theoretical advantages but were not feasible.

Failure to demonstrate striking differences between cancer and benign cells is not surprising. A continuing study of tumors and analogous nonneoplastic tissue by various cytophysical and cytochemical techniques has shown no qualitative difference between these two classes. Batteries of cytochemical tests,[5] photometry,[4] and interference microscopy[6] have been employed. This study has added another method of investigation. Qualitative differences have been noted which are not sharply diagnostic. Cell growth and maturation rather than benignancy or malignancy apparently account for the differences.

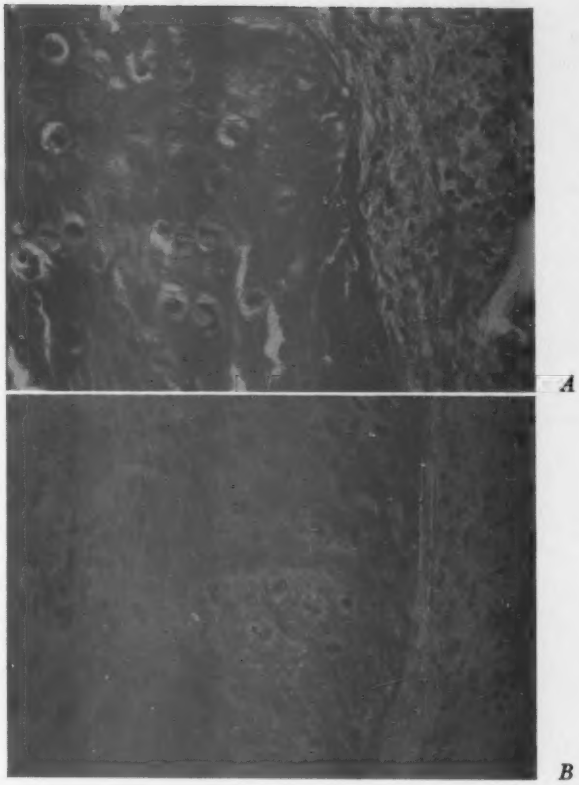

Fig. 7. Intraepithelial carcinoma (×330; reduced ⅓). *A*, Methylene blue, pH 8. Note intense staining of mitotic figures, and moderate staining of cytoplasmic elements. *B*, Methylene blue, pH 4. Mitotic figures retain considerable affinity for the stain, while other elements are much paler.

Summary

In a continuing program of study of cervical carcinoma by special cell techniques, sections from cases of squamous metaplasia, atypical hyperplasia, carcinoma in situ, and invasive carcinoma of the cervix were stained with methylene blue and light green in a range of pH.

Staining intensity of various cellular structures in normal and abnormal epithelium was recorded on an arbitrary scale.

Proteins can be characterized by their staining reaction in a pH range. Binding with basic dye was more intense in an alkaline medium. Binding with an acid dye was more intense in an acid medium.

Mitoses stained with basic dye in relatively acid medium.

No difference was demonstrable between normal and cancer cells with this approach.

Considering morphology and especially hyperchromatism, atypical hyperplasia

shared the characteristics of invasive and in situ cancer, while metaplastic epithelium more closely resembled the character of normal epithelium.

The technical assistance of Mrs. Elizabeth Anderson and Miss Gladys Clark in preparation of sections and of Mr. Gene Nabi in preparation of graphs and photomicrographs is gratefully acknowledged.

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Bilateral primary ovarian carcinomas

Case report

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BILATERAL primary ovarian carcinomas of different cell types are relatively rare. Search of the literature has failed to reveal a case similar to the one reported here.

M. B., a 58-year-old gravida i, para i, white woman, was admitted on Sept. 17, 1959, with complaints of pelvic discomfort, constipation, and progressive abdominal enlargement. One and one half years prior to admission, the patient was informed of the presence of a pelvic mass discovered on routine examination. Past history and family history were unremarkable. There were no significant complaints referable to the cardiovascular digestive, and genitourinary systems. The patient had been delivered of a 12½ pound infant in 1934 after a long and difficult labor. Since an uneventful menopause which occurred 9 years previously, the patient had been completely amenorrheic. On admission, the blood pressure was 120/80 and pulse 84 per minute. Physical examination revealed a very obese middle-aged woman in no distress. No nevi were detected. The breasts were pendulous, nontender, and devoid of palpable masses. A large, irregular hard mass extending to the umbilicus and seemingly arising from the pelvis was palpated through the abdominal wall. The hemoglobin level was 10.5, hematocrit determination 37, white blood count 3,850 with a normal differential. Urinalysis was within normal limits. Intravenous pyelogram revealed normal renal function with no compression or distortion of the ureters. The ECG was normal.

From the Department of Obstetrics and Gynecology, Jefferson Medical College.

Pelvic examination under anesthesia revealed an irregular hard mass extending from the pelvis up to the umbilicus, more prominent on the left side.

At operation, the lower abdominal cavity was entered through a midline incision. The liver, kidneys, and gall bladder were normal to palpation. The pelvic mass represented a greatly enlarged mutinodular left ovary that was adherent to the sigmoid colon, which was displaced toward the midline. The right ovary was of normal size but also adherent to the lateral walls of the sigmoid. The uterus was not enlarged. A total hysterectomy and bilateral salpingo-oophorectomy were performed. During the process of separating the adherent ovaries, a small perforation was made in the sigmoid colon, which was

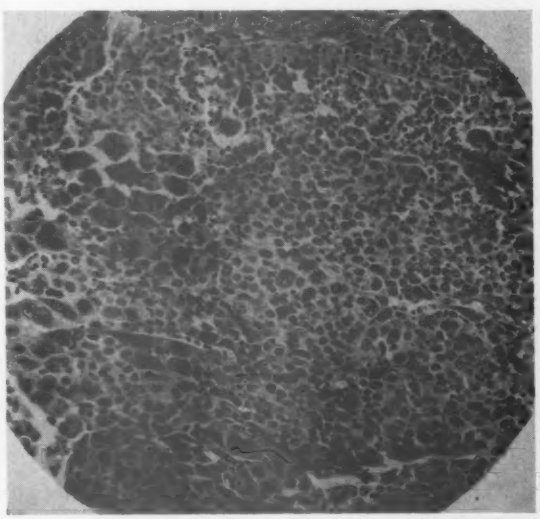

Fig. 1. High-power field of the left ovarian carcinoma.

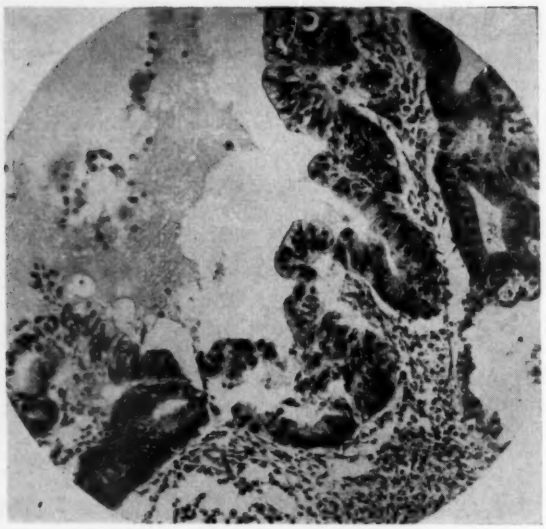

Fig. 2. A well-differentiated low-grade adenocarcinoma of the right ovary.

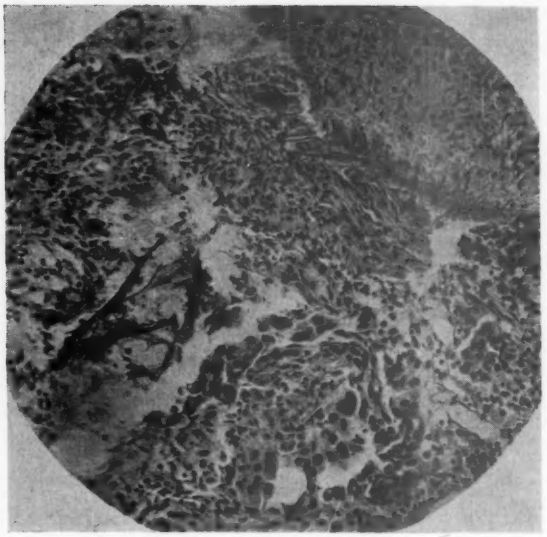

Fig. 3. Focal left ovarian metastatic collections of anaplastic cells found in the right ovary.

repaired. The bladder flap was attached to the serosa of the sigmoid above the point of perforation and a Penrose drain was placed in the cul-de-sac and brought through the vaginal cuff.

Pathology. The uterus weighed 90 grams and measured 9 by 5 by 4 cm. It contained several small intramural myomas and an endometrial polyp. Mutiple sections revealed no histologic evidence of malignancy.

The left adnexal mass weighed 750 grams and measured 15 by 14 by 8 cm. The external surface was lobulated, smooth, and purplish red in appearance. The tumor cut with a fairly firm consistency and the cut surface appeared yellowish tan with focal areas of hemorrhage and necrosis. Histologic sections revealed a high-grade medullary carcinoma of the left ovary (Fig. 1).

The right ovary measured 3 by 3 by 1 cm. and had a firm consistency. The external surface was irregular, smooth, and mottled reddish yellow in appearance. There were several small cystic cavities measuring 1 by 1 cm. seen on the cut surface. Histologic sections revealed a low-grade adenocarcinoma of the right ovary (Fig. 2). In addition, foci of tumor cells with the same histologic features as those from the left ovary (Fig. 3) were found in some sections of the right ovary. Several fibroadenomas were also present in the right ovary.

On the fifth postoperative day, fecal material was found to be draining through the vagina. The drainage subsided spontaneously and the Penrose drain and sutures were removed on the seventh postoperative day. Cobalt beam teletherapy was started on the eighth postoperative day. She was discharged in good condition 22 days after the operation.

Comment

In view of the highly anaplastic nature of the left ovarian carcinoma, a very careful physical examination was done to rule out a primary breast carcinoma or a malignant melanoma. There was no clinical evidence suggesting the presence of the latter two entities. The focal collections of anaplastic malignant cells in the right ovary was explained on the basis of lymphatic spread from the left ovary. The adenocarcinoma of the right ovary revealed no gross or histologic characteristics of a Krukenberg tumor. The patient presented no gastrointestinal complaints, and roentgenologic evaluation of the gastrointestinal tract revealed no abnormalities.

Since no extrapelvic or uterine primary malignancies could be found, the ovarian neoplasms represented primary carcinomas.

Summary

A case is presented of a patient with a primary high-grade medullary carcinoma of the left ovary with metastasis to the right ovary and a primary low-grade adenocarcinoma of the right ovary.

Equilateral distribution of ovarian tumors

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A MORE frequent occurrence of ovarian neoplasms in the left than the right ovary has been suggested by several authors.[1, 2] On the basis of such data the prophylactic removal of the left ovary at the time of hysterectomy in premenopausal patients has been proposed by Siddall and Levine[1] as a means of decreasing the incidence of subsequent ovarian tumors and still avoiding castration.

It is not within the scope of this paper to discuss the pros and cons of prophylactic removal of ovaries in premenopausal patients being operated upon for benign conditions requiring hysterectomy. Suffice it to say, however, that in the case of such patients who are 30 years of age and older, opinions vary from ablation of all ovarian tissue to preservation of normal ovaries at the time of hysterectomy.[3]

If tumors involving the left ovary could be shown to be statistically more frequent than those of the right ovary there might be merit in routine prophylactic left oophorectomy in premenopausal patients at the time hysterectomy is performed. Such a procedure would then offer a significant reduction in the incidence of further ovarian neoplasms while maintaining a good portion of the major source of estrogen.

For this reason we have reviewed our cases of ovarian tumors not only as an entire series, but also as individual groups to determine if there was a predilection for one side or another.

Material

All of the material is from the files of the laboratory of the Department of Obstetrics and Gynecology of Northwestern University Medical School. Follicle, corpus luteum, germinal inclusion cysts, and metastatic lesions were eliminated, and the cystomas were included only when there was a clearly serous or mucinous epithelial pattern in a unilocular cyst. All other ovarian tumors were evaluated except those occurring in patients with a history of a previous oophorectomy. Because some of the patients had more than one type of ovarian tumor, the number of tumors exceeded the number of patients.

The gross and microscopy reports were reviewed to determine the side of origin of each tumor. There were 154 instances where the side on which the neoplasm existed could not be determined because there was inadequate description of the gross specimen or there was insufficient clinical information, or in the case of microscopic-sized lesions the side from which blocks were cut was not stated. These cases were eliminated from the series.

Microscopy slides were reviewed except in a few cases where they were not avail-

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**Aided in part by the Josiah Macy, Jr., Foundation Scholarships to Medical Students for Studies in Reproduction, and by a Cancer Control Grant from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.*

Table I. Side of origin of all ovarian tumors in the series

Right	353
Left	398
Bilateral	111
Total	862

able, and a few specimens were omitted when the original diagnosis could not be confirmed.

Findings

There were 1,016 ovarian tumors of all types and 862 of them were available for the study in that the side of origin could be established.

In Table I the distribution of the entire group of ovarian neoplasms is demonstrated. While these figures reveal an over-all increase in the incidence of tumors of the left ovary, statistical evaluation indicated that no significant difference existed from the expected value of 50 per cent, or 375 tumors on each side, as the value for P was 0.26. Similar analysis of the 500 cases presented by Siddall and Levine[1] gave a value for P of 0.07, which again implied that the increased number of tumors involving the left ovary was not significantly different from the expected value of 50 per cent. Evaluation of the smaller series of Grimes, Bartholomew, Colvin, Fish, and Lester,[2] which included only those cases of ovarian tumor associated with pregnancy, indicated that the increase in the left sided tumors was of borderline significance inasmuch as P was 0.03.

Table II shows the frequency of the side of origin of the various tumor types making up the entire sample. Several types of tumor, particularly the cystomas and cystadenomas, showed a moderate numerical increase on the left side, but in no case was the difference significant. The cystomas had a P value of 0.08, and in each of the other types the value for P was more than 0.2.

In Table III the cystomas and cystadenomas have been combined. There again appears to be an increase in tumors of the left ovary; however, statistical evaluation did not bear this out as the P value was 0.07.

The entire group of benign tumors is

Table II. Side of origin of various tumor types making up the entire sample

	Right	*Left*	*Bilateral*	*Total*
Cystomas	64	95	15	174
Serous	56	82	12	150
Mucinous	8	13	3	24
Cystadenomas	92	110	29	231
Serous	50	54	23	127
Mucinous	42	56	6	104
Connective tissue	34	43	5	82
Fibromas	21	24	1	46
Fibromyomas	1	4	–	5
Fibroadenomas	12	15	4	31
Teratoid, benign	95	84	25	204
Brenner tumors	6	9	2	17
Dysgerminomas	1	2	–	3
Functional tumors	22	18	3	43
Granulosa-theca cell	22	18	2	42
Arrhenoblastoma	–	–	1	1
Adenocarcinoma	9	18	14	41
Cystadenocarcinoma	29	16	17	62
Serous	19	13	14	46
Mucinous	10	3	3	16
Teratoid, malignant	–	2	1	3
Sarcoma	–	1	–	1
Choriocarcinoma	1	–	–	1
Total cases	353	398	111	862

shown in Table IV, and again no real difference could be demonstrated. P was 0.16.

Table V reveals the side of occurrence of the malignant group of tumors. Here the difference between the left and right sides is small and certainly not significant. The increased frequency of bilateral tumors is about as expected.

Comment

Neither our series of 862 ovarian tumors nor the somewhat smaller series of Siddall and Levine[1] and Grimes and associates[2] could be shown to contain a statistically significant increase in the number of tumors involving the left ovary over the expected value of 50 per cent. Combination of the above three series of cases as shown in Table VI does indicate a significant increase on the left side with a P value of 0.006. While this figure is in part due to the larger number of cases involved, we feel that it is mostly due to bias in selection of the groups of cases which has produced misleading statistics. In addition, at least two sizeable series of cases of benign cystic teratomas[4] and mucinous cystadenomas and mucinous cystadenocarcinomas[5] have indicated about equal occurrence in the left and right ovaries, although the actual figures on each side were not mentioned.

Even if a slight predilection of tumors for the left or right ovary could be demonstrated, the therapeutic advantage of oophorectomy on the predominant side would be infinitesimally small. Although he had no figures for patients over the age of 40, Randall[6] noted that 14 of 1,000 women over the age of 50 will develop an ovarian neoplasm, which in 8 cases will be malignant. Thus, if prophylactic unilateral oophorectomy were performed, one might expect a decrease of something less than 50 per cent in the cases in which ovarian tumors later develop. However, the advantage of excising the side of most frequent involvement as opposed to the opposite side might be expected at best to be 1 or 2 cases per 1,000.

In the absence of any apparent significant increase in the number of ovarian tumors involving the left or right ovaries, the side on which unilateral oophorectomy was performed would not alter the incidence of subsequent ovarian neoplasms. In general, while unilateral prophylactic oophorectomy might have some advantages, the decision as to oophorectomy of any type should be one of individual evaluation of the case and the pathologic lesion at hand.

Table III. Frequency of occurrence of the combined group of cystomas and cystadenomas

Right	156
Left	205
Bilateral	44
Total	405

Table IV. Frequency of occurrence of the benign tumors as a group

Right	291
Left	341
Bilateral	76
Total	708

Table V. Frequency of occurrence of the malignant tumors as a group

Right	62
Left	57
Bilateral	35
Total	154

Table VI. Present series combined with those of other authors*

	Right	*Left*	*Bilateral*	*Total*
Siddall and Levine[1]	188	241	53	482
Grimes and associates[2]	67	109	7	183
Farrar and Bryan	353	398	111	862
Total cases	608	748	171	1,527

*Cases omitted when side of origin not known.

Summary

A series of 862 ovarian tumors was evaluated.

There was no statistical difference in the number of cases involving the left and right ovaries.

There appears to be no advantage in removal of one ovary over its opposite as a means of further decreasing the incidence of subsequent ovarian tumors.

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Bilateral Brenner tumors of the ovary

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BRENNER tumors are being reported with increasing frequency, but bilateral Brenner tumors are relatively rare. Recently Bungard and Haug[1] reported a case of bilateral Brenner tumors and considered it to be the seventeenth reported in the literature. They did not, however, include one case of Peale's,[2] one of de Queiroz's,[3] and another of Stöckl's.[4] In addition, 2 reported by Postoloff and Sotto,[5] 2 described by Teoh,[6] and 3 included by Reagan[7] were not mentioned. This makes a total of 27 bilateral Brenner tumors in the literature, and while this number probably does not include all such cases it must at least represent the majority.

We should like to add 2 more to the above 27, making a total of approximately 29 reported to date. Since slightly more than 400 Brenner tumors have been reported,[8] the incidence of bilaterality appears to be about 7 per cent. This figure is undoubtedly high since bilateral Brenner tumors are of more interest and would tend to be reported while the unilateral variety would tend to be ignored.

Case reports

Case 1 (NUMS gyne. path. 20131). This 48-year-old white gravida ii, para 0, was 4 years postmenopausal. She complained of pressure in the right lower abdomen with occasional nausea and vomiting of 2 months' duration. Past history was noncontributory. General physical examination and laboratory findings were negative, but on bimanual pelvic examination an irregular mass was found and was thought to be the uterus with a myoma on the right wall. No adnexal masses were described.

At operation the uterus and tubes were found to be normal. The left ovary was hard, smooth, and twice normal size. The right ovary was also hard and approximately 8 cm. in diameter. It was adherent to the peritoneum of the cul-de-sac. A total hysterectomy and bilateral salpingo-oophorectomy were performed. On bisection the left ovary was found to be almost completely replaced by a sharply demarcated, firm, smooth, yellow mass 2.7 cm. in its greater diameter. The right ovary was replaced by a similarly appearing tumor 8.5 cm. in greatest diameter.

Microscopically there was chronic cystic cervicitis. The endometrium and tubes were atrophic.

Nine paraffin blocks were prepared from the right ovary and stained with hematoxylin and eosin. In addition, one of the blocks was stained by Milligan's trichrome, reticulum (Wilder's method), periodic acid–Schiff, and periodic acid–Schiff with diastase digestion techniques. The sections stained with hematoxylin and eosin were quite similar. The Brenner tumor was slightly lobulated and appeared to have completely replaced the ovary since no normal ovarian tissue was identified. The surface of the tumor was covered by a thick layer of loose, rather vascular connective tissue. The epithelial nests were mostly small and round or oval. Rarely, larger, tubular and branching nests were seen (Fig. 1). Occasional small, cystic spaces were identified which contained mucin.

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Financed in part by a cancer control grant from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

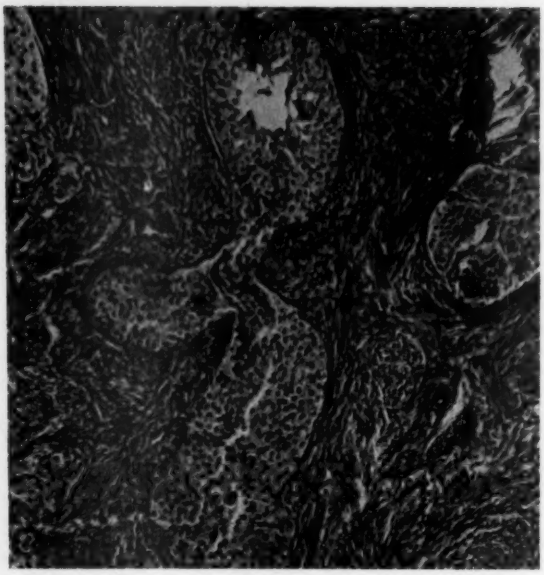

Fig. 1. Case No. 20131. Right ovary. Variably sized and occasionally branching epithelial nests are surrounded by a predominantly fibrous stroma. (×100; reduced ¼.)

Fig. 2. Case No. 20131. Right ovary. Reticulum stain. Reticulum fibers are seen penetrating an epithelial nest. This feature suggests a stromal origin of the tumor. (×645; reduced ¼.)

No intracellular mucin or mucinous epithelium was noted. Trichrome stain revealed a dense and predominantly fibrous stroma with some hyalinized areas. Reticulum was diffuse with some concentration about the epithelial nests. In some areas reticulum fibers penetrated into the nests and tended to surround individual cells (Fig. 2). Cellular or theca-like elements were absent in the stroma and no basement membrane was seen about the epithelial nests. Of interest was the presence of small glycogen droplets scattered throughout the epithelial nests on periodic acid–Schiff stain (which were not present after diastase digestion).

Six blocks were prepared from the smaller left ovary and stained with hematoxylin and eosin. As with the right ovary, similar special staining preparations were made from one block.

This smaller, slightly lobulated tumor was covered by a generous portion of inactive appearing ovarian cortex. In one area, where the tumor approached the hilum of the ovary, the rete ovarii was prominent, but was not continuous with the tumor. A small epithelial plaque was seen on the adjacent mesosalpinx, the cells of which were dissimilar to the cells of the epithelial nests.

The epithelial nests in this tumor were somewhat larger than in the tumor of the right ovary. They tended in many cases to form irregular columns, which were occasionally branching (Fig. 3). The nests were solid except for a rare one which showed single small spaces containing mucin. There was no intracellular mucin. As in the right ovary, glycogen droplets were prominent in the nests. A basement membrane was not seen.

The stroma was dense and fibrous. The reticulum fibers accumulated about the epithelial nests and in some areas penetrated the nests and tended to surround individual cells. Material from these tumors, unfortunately, was not saved for fat stains.

For reasons discussed in a previous publication by one of us,[9] both right and left Brenner tumors were considered to be of ovarian stromal origin.

Case 2* (NUMS gyne. path. 29360). The patient was 47 years old, gravida iii, para iii. She complained of a dull, aching, low abdom-

*The gross and clinical material from this case was furnished to us by Dr. W. F. Dillon.

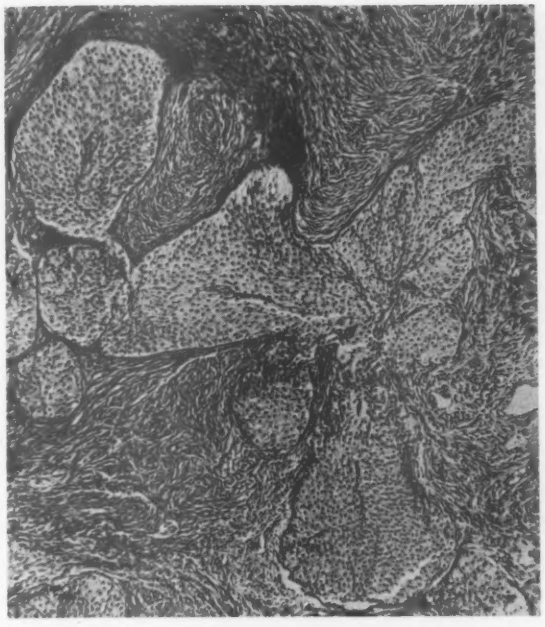

Fig. 3. Case No. 20131. Left ovary. Large epithelial nests forming irregular columns are seen in a dense fibrous stroma. (×100; reduced ⅓.)

inal pain of 3 months' duration. Her last menstrual period had been 26 days prior to operation and her menstrual periods had been normal with no intermenstrual bleeding. General physical examination and laboratory findings were negative. On pelvic examination 10 months prior to admission the left ovary was noted to be cystic and slightly enlarged. On examination just prior to admission the left ovary was noted to be hard and mobile and measured 7.5 cm. in diameter. The right ovary was not palpable. The uterus was anterior and normal. At operation the pelvic findings were confirmed. A total hysterectomy and bilateral salpingo-oophorectomy were performed.

Grossly the left ovary was replaced by a hard white tumor 7.5 cm. in diameter. A similar hard white nodule about 1.5 cm. in diameter was found at one pole of the right ovary.

Microscopically there was chronic cervicitis with slight metaplasia and areas of focal adenomatous hyperplasia of endocervical glands. The endometrium was late secretory and early

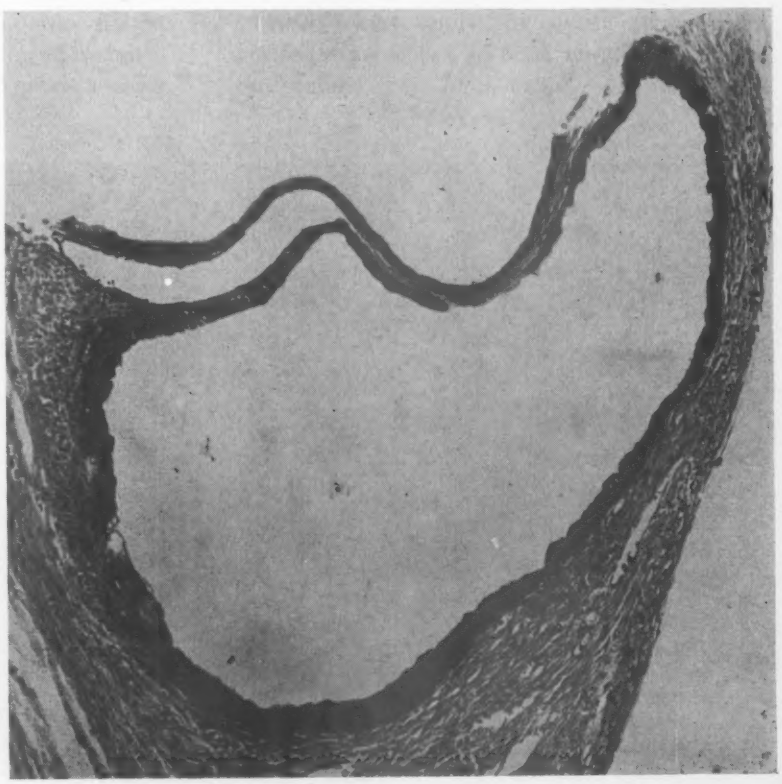

Fig. 4. Case No. 29360. Left ovary. PAS with diastase digest preparation. One of several cystic spaces lined by mucin-positive columnar cells. This area represents a small mucinous cystadenoma. (×150; reduced ⅛.)

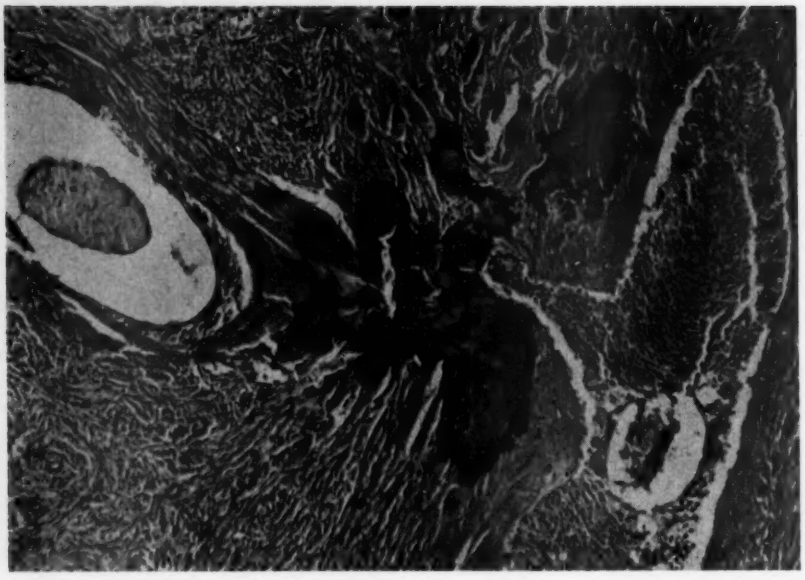

Fig. 5. Case No. 29360. Left ovary. The dense fibrous stroma contains hyalinized and calcified areas. (×165; reduced ⅛.)

menstrual. There was adenomyosis and a small intramural myoma.

Three paraffin blocks were prepared from the left ovary. Hematoxylin and eosin, Milligan's trichrome, reticulum (Wilder's method), periodic acid—Schiff, and periodic acid—Schiff with diastase digestion preparations were made from each block. In the first block adjacent to, but separate from, a Brenner tumor were 2 small cystic spaces lined by mucinous appearing epithelium. The presence of intracellular mucin was confirmed by a periodic acid–Schiff diastase digest preparation. This area obviously represented a small mucinous cystadenoma (Fig. 4).

The Brenner tumor contained many large islands and cords of typical Brenner cells. Many of the islands were cystic and the spaces contained mucin. Numerous Brenner cells, especially those lining the cavity, contained intracellular mucin. No basement membrane was present about the epithelial nests. The surround-

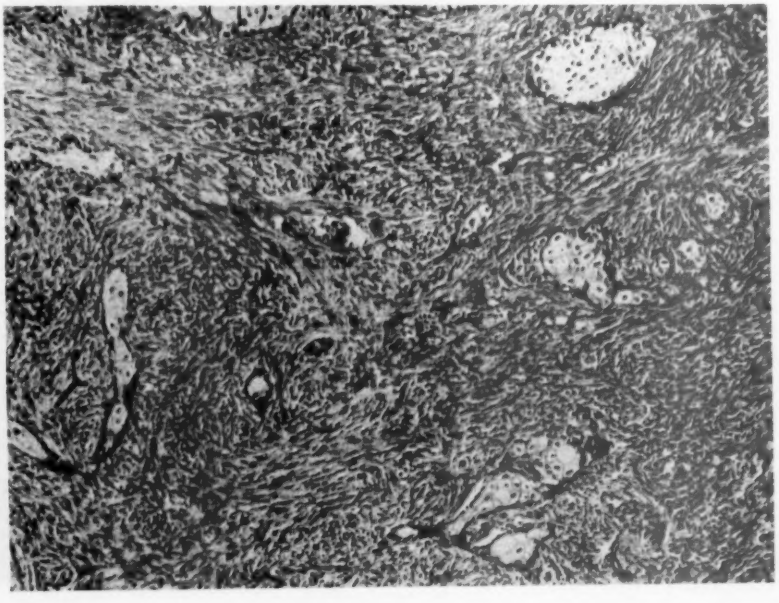

Fig. 6. Case No. 29360. Left ovary. A small cortical tumor shows scattered, tiny, occasionally cystic Brenner nests. The stroma is identical to that of the adjacent normal cortex (not shown). (×100; reduced ⅛.)

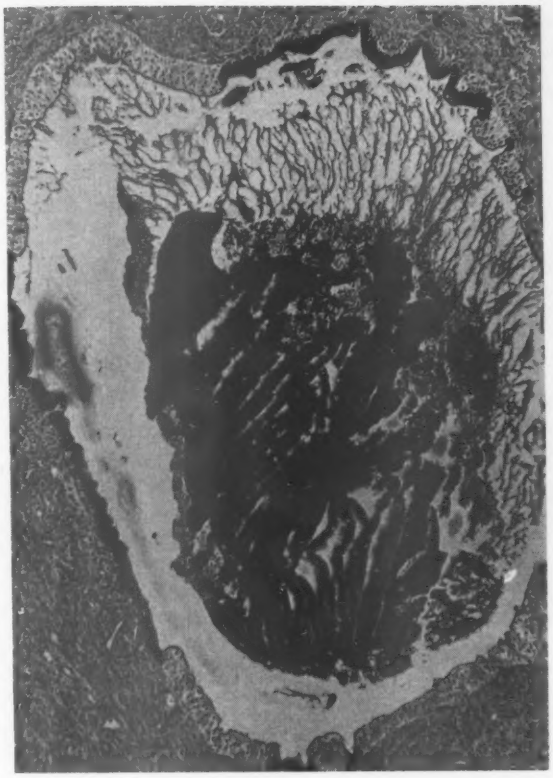

Fig. 7. Case No. 29360. Left ovary. PAS with diastase digest preparation. A cystic Brenner nest is lined by both Brenner and mucinous type epithelia. (×100; reduced ⅔.)

ing stroma was quite cellular. The reticulum fibers were moderate in amount and tended to be condensed around the epithelial masses. There was, however, no penetration of reticulum fibers into and around epithelial elements as in the first case.

The next block showed part of the same tumor, although there seemed to be more stroma which tended in some areas to be hyalinized with areas of calcification (Fig. 5). Entirely separate and in the overlying cortex there was what appeared to be a second tumor (Fig. 6). It was composed of scattered, small, irregular cords and nests of Brenner type cells. Some of the nests were cystic and contained mucin. Occasional Brenner cells contained intracellular mucin. The stroma was similar to ovarian cortex. Reticulum fibers were prominent with concentration about the epithelial areas. The recticulum fibers did not penetrate into epithelial areas and surround individual cells.

The third block was similar to the first except there was one fairly large, cystic epithelial nest which was lined in part by Brenner type epithelium and in part by mucinous type epithelium (Figs. 7 and 8).

Three blocks were prepared from the right ovary. The first block contained 3 apparently separate Brenner tumors, 2 of which were in

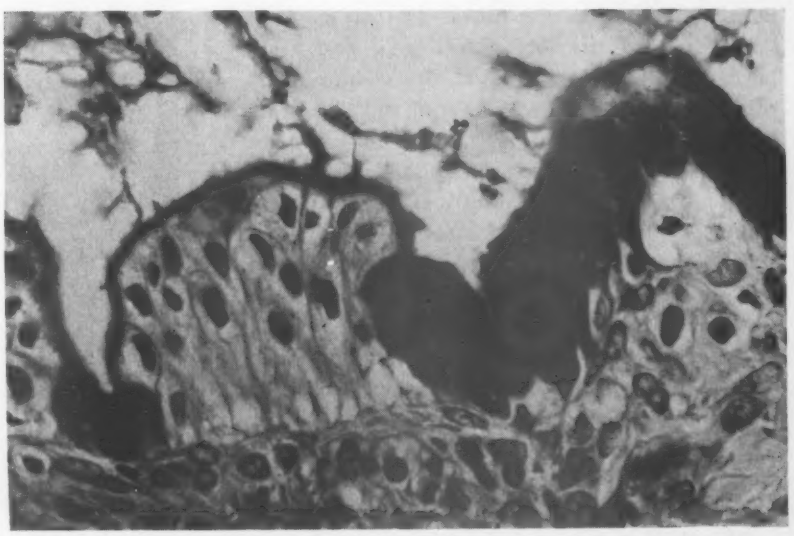

Fig. 8. Case No. 29360. Left ovary. High power of Fig. 7. The transition of one epithelial type to another is very distinct. (×645; reduced ¼.)

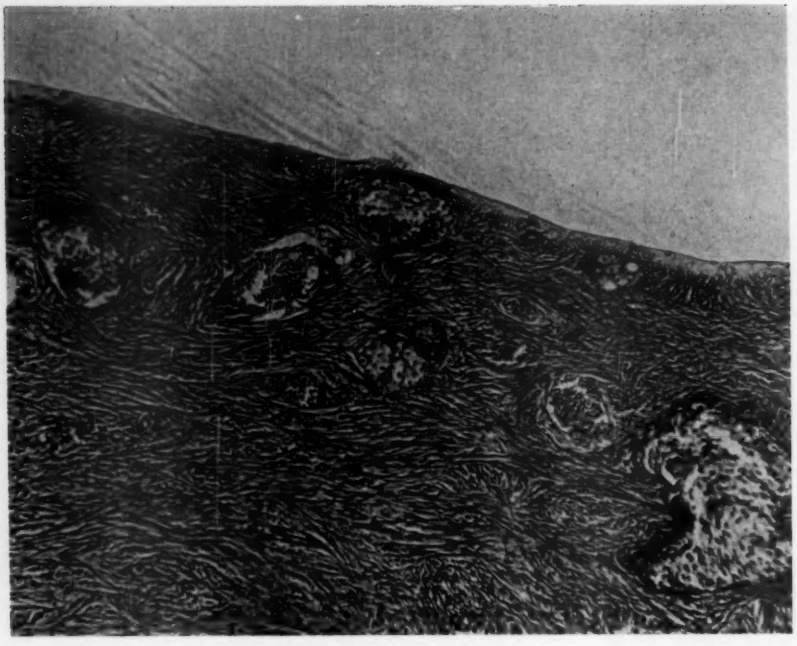

Fig. 9. Case No. 29360. Right ovary. A small cortical Brenner tumor. A definite transition of germinal epithelium to a Brenner nest cannot be demonstrated. (×100; reduced 1/10.)

the cortex and the other in the medullary portion of the ovary. The larger and grossly visible tumor had Brenner nests and cords which approached to within a few microns of the surface of the ovary, but no continuity with germinal epithelium (which was traumatically absent) could be established (Fig. 9). The nests and cords tended to be small and scattered. Some were cystic and contained mucin but no intracellular mucin was noted. The stroma contained a large amount of collagen, and areas of calcification were present. Reticulum fibers were evenly distributed and did not penetrate into the epithelial masses. No basement membrane was present about the epithelial areas.

The second and apparently separate cortical Brenner tumor contained smaller islands and cords. The stroma contained less collagen and was more "cellular." No calcium was present. Reticulum did not penetrate into the epithelial areas. This smaller tumor was separated from the grossly evident tumor by a small area of normal cortex. Unfortunately, serial blocks were not obtained of the ovary, and we do not know but what this second tumor was a circuitous tongue-like continuation of the first.

The third tumor was deep in the medullary region of the ovary (Fig. 10) and consisted of several solid epithelial cords and nests and

Fig. 10. Case No. 29360. Right ovary. A Brenner tumor in the medullary region of the ovary. (×100; reduced 1/4.)

other large cystic spaces with flattened epithelium. The cystic spaces contained mucin as did the cells which lined the spaces. The stroma was cellular and the reticulum moderate in amount. No basement membrane was seen. This particular tumor suggested an origin from rete ovarii.[9] although no normal rete was present in the section.

The second slide contained the grossly evident tumor and the findings were essentially the same as previously described. The third contained normal ovarian tissue.

Fat stains were made from the left ovarian tumor. Occasional fat globules were seen in stromal cells and in a few Brenner cells. This fat was not doubly refractive and most likely represented a degenerative phenomenon.

Comment

It is obvious that we were errant in handling the tissues in Case 2. After preparation of the paraffin blocks and the frozen sections the tissues were discarded. Ideally, serial blocks should have been made and if necessary step serial sections. Only then could we be absolutely certain that the left ovary contained 3 separate tumors including a small mucinous cystadenoma and 2 Brenner tumors, and the right ovary 3 separate Brenner tumors. As it is we cannot rule out the unlikely possibility of a circuitous continuity among the various Brenner tumors in each ovary that was not evident in our blocks. At any rate, one thing is certain: the patient had bilateral Brenner tumors.

The co-existence of Brenner tumors and mucinous cystadenoma with areas of transition of mucinous to Brenner type epithelium has recently been reviewed by Freda and Montimurro.[10] They reported 2 such cases. Previous to their article such a transition had been reported by von Szathmary[11] in 2 cases, Held[12] in one, Plaut[13, 14] in one, and Biggart and Macafee[15] in one. Including our Case 2, mucinous cystadenomas have been associated with 4 of 28 Brenner tumors that we have available for study. Continuity between mucinous and Brenner type epithelium was found only in the present Case 2.

Summary

Two cases have been presented in which there were Brenner tumors in each ovary.

This makes an approximate total of 29 instances of bilateral Brenner tumors that have been reported.

In our first case the bilateral Brenner tumors were similar in appearance and of ovarian stromal origin.

In the second case there was apparently a mucinous cystadenoma and 2 separate Brenner tumors in the left ovary and 3 Brenner tumors in the right ovary. The word "apparently" is used because serial blocks of the ovaries were not obtained. In the left ovary there was an area in a Brenner tumor where a cystic cavity was lined in part by mucinous and in part by Brenner epithelium.

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The mode of infection and reinfection in yeast vulvovaginitis

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SINCE the virtual rediscovery of "mycotic vulvovaginitis" by Plass, Hesseltine, and Borts,[3] evidence has accumulated that yeast organisms frequently occur in the human vagina and under certain circumstances (dependent on the species of the yeast and the predisposition of the host) may cause disease.

Little attention has so far been given to the question of the source from which yeast organisms, harmless or not, may enter the vagina. This question involves the important problem of the mode of infection and reinfection in yeast vulvovaginitis, the better understanding of which should be helpful in the treatment of this disease and particularly in the prevention of relapses. Feces[7] and urine[2] may harbor yeast species which are simultaneously present in the vagina of the same woman, and these have been incriminated as sources of infection.

It is the purpose of this paper to report on our studies with regard to feces and urine as possible sources of vaginal yeast organisms.

The word "yeast" is here used in the sense of contemporary American[6] and European[1] taxonomists to include also budding fungi of genera like *Candida, Torulopsis,* and *Cryptococcus,* which lack the capability of sexual reproduction and as a group have been called "yeast-like" fungi by many authors.

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Part of this work was subsidized by the Instituto de Alta Cultura, Lisbon.

Methods

Isolation of yeasts. Vaginal cultures were done with a loopful of vaginal discharge collected from the posterior fornix or from lesions of the vaginal wall.

Fecal cultures were prepared from feces collected by the patients not more than a few hours earlier. To avoid yeast organisms which might have contaminated the specimen during (vaginal discharge, urine) or after (air, flies, etc.) its production, a solid fecal particle was opened with flamed instruments and a loopful of material taken from the center.

For urine cultures the vestibulum was cleaned with a disinfectant from the meatus toward the introitus and urine collected with a catheter. About 5 c.c. of the first and 5 c.c. of the last urine were pooled and centrifuged at 3,000 r.p.m. for 10 minutes. The whole sediment was used for inoculation.

Material for cultures was inoculated into tubes containing broth of the following composition: glucose, 2 per cent; yeast extract (Difco) 0.5 per cent; peptone, 1 per cent; and distilled water. To limit bacterial growth, 50 units of penicillin per cubic centimeter and 100 units of streptomycin per cubic centimeter had been added to the

broth. To exclude all yeast organisms which do not thrive at body temperature and therefore cannot be considered inhabitants of the intestinal or urogenital tract, the tubes were incubated at 37° C. After 4 to 6 days of incubation the tubes were shaken and a loopful of the broth was streaked on plates of the following composition: glucose, 2 per cent; yeast extract (Difco), 0.5 per cent; peptone, 1 per cent; agar, 2 per cent; and distilled water. To discourage bacterial growth, the medium was adjusted to pH 4.5 with lactic acid. The plates were incubated at 37° C. From each type of yeast colony which appeared on the plates a single one was isolated and, when necessary, purified by plating or passage through media containing antibiotics.

Identification of yeasts. The isolated yeast organisms were classified according to the system of Lodder and Kreger-van Rij.[1] All could be identified with species described in the latter monograph, except for 12 fecal strains which were found identical with *Saccharomyces italieus* var. *melibiosi,* described by van Uden and Assis-Lopes.[5]

The properties of the isolated organisms were studied by the following methods:

A. Growth in liquid medium. According to the method of Lodder and Kreger-van Rij[1] but with the following medium: glucose, 2 per cent; yeast extract (Difco), 0.5 per cent; peptone, 1 per cent; and distilled water. The streak culture was studied on a medium containing glucose, 2 per cent; yeast extract (Difco), 0.5 per cent; peptone, 1 per cent; agar, 2 per cent; and distilled water.

B. Formation of pseudomycelium. On Dalmau plates[6] with the same medium as for the streak culture. In doubtful cases potato glucose agar (Difco) or corn meal agar (Difco) was also used.

C. Sporulation. According to the method of Lodder and Kreger-van Rij.[1]

D. Fermentation. Glucose, galactose, sucrose, maltose, and lactose according to the method of Wickerhan[6]; raffinose according to the method of van Uden.[4]

E. Assimilation. According to Wickerham's[6] technique. The following compounds were used: D-glucose, D-galactose, sucrose, maltose, lactose, raffinose, L-arabinose, D-xylose, ethanol, glycerol, D-mannitol, D-sorbitol, inositol, inulin, soluble starch, and potassium nitrate.

Treatment. Women who harbored yeast organisms in the vagina, and whose feces or urine had been cultured for yeasts, were submitted to local vaginal treatment so that the persistence of yeasts in or their disappearance from urine or feces could be studied after elimination of the same species from the vagina.

Treatment consisted in the daily vaginal application of either dichloroxychinaldine (Chlorquinaldol) or Trichomycin. The daily dose of the former consisted of 2 vaginal tablets of 50 mg. each, of the latter of 2 vaginal tablets of 50,000 units each.

In most cases 5 to 10 days of treatment were sufficient to eliminate yeast organisms from the vagina.

Control cultures from the vagina were taken 3 days after the last application of drugs and whenever urine or fecal cultures were repeated.

Results and comments

The possible importance of feces as a source of vaginal yeast organisms was

Table I. Incidence of yeast species in the vagina in 481 women

Species	*271 non-pregnant women with vulvovaginal symptoms*	*210 unselected pregnant women*	*Total of 481 women*
C. albicans	63	42	105
T. glabrata	15	15	30
C. krusei	4	3	7
C. albicans and *T. glabrata**	8	1	9
C. albicans and *C. krusei**	1	0	1
C. parapsilosis	1	3	4
C. tropicalis	2	0	2
C. stellatoidea	1	2	3
C. guilliermondii	0	3	3
S. carlsbergensis	1	0	1
Negative	193	143	336

*Counted also separately under the respective species.

Table II. Yeast organisms isolated from the feces of 225 women

C. albicans	85
C. krusei	35
C. parapsilosis	26
C. tropicalis	26
C. utilis	6
C. guilliermondii	3
T. glabrata	40
S. cerevisiae	31
S. carlsbergensis	13
S. italieus var. *melibiosi*	12
Pichia membranaefaciens	39
Pichia fermentans	8
Hansenula anomala	2
Trichosporon cutaneum	7
Not classified	9

studied in a group of 481 women composed of 210 unselected pregnant patients and 271 gynecologic patients with vulvovaginal symptoms. The yeast organisms obtained from the vaginas of these women when seen for the first time are listed in Table I. The usual preponderance of *Candida albicans* was found. Among the other species isolated, *Torulopsis glabrata* was relatively frequent. Most of the women who harbored the latter species were symptomless and none had clear subjective or objective symptoms of yeast vulvovaginitis. Whereas *C. albicans* is a proved potential pathogen, *T. glabrata* is probably completely harmless.

As these two species occurred with appreciable frequency in the vagina, correlation studies with fecal yeast organisms could be done.

In 225 women of the above-mentioned group it was possible to perform fecal cultures. The yeast organisms which were isolated from the feces on the first occasion can be seen from Table II. As shown in Table III, it was found that of the 55 women with positive vaginal cultures for *C. albicans* 76 per cent harbored the same yeast in their feces, whereas of 170 women with negative vaginal cultures only 25 per cent had positive fecal cultures for *C. albicans.* A similar situation was found with regard to *T. glabrata;* 82 per cent of 21 women with positive vaginal cultures also had positive fecal cultures, whereas of the 204 negative controls only 11 per cent had *T. glabrata* in the feces. These results show correlation of a high degree between the occurrences of certain yeast species in the vagina and their occurrence in the intestinal tract.

Should the intestinal tract really constitute a source from which the vagina is infected or reinfected with certain yeast species, these species should be present in the intestine before and after their occurrence in the vagina. The latter supposition was studied by making fecal cultures from the same women after their vaginas had been made yeast-free by specific treatment. As can be seen from the last two columns

Table III. Correlation between vaginal and intestinal yeast organisms in 225 women

	Feces		
Vagina	*Simultaneous with first vaginal culture*	*One week after completion of local vaginal treatment*	*Three weeks after completion of local vaginal treatment*
Candida albicans			
55 positives	42 positives (76%)	38 positives	41 positives
	13 negatives	17 negatives	14 negatives
170 negatives	43 positives (25%)		
	127 negatives		
Torulopsis glabrata			
21 positives	18 positives (82%)	19 positives	19 positives
	3 negatives	2 negatives	2 negatives
204 negatives	22 positives (11%)		
	182 negatives		

of Table III, the fecal incidences of *C. albicans* and *T. glabrata* were not significantly altered by local vaginal treatment. We conclude from these findings that women who harbor *C. albicans* or *T. glabrata* in their intestinal tracts are more likely to suffer vaginal infection by these yeasts than other women. Furthermore in agreement with Yo Bwan Hie,[7] we think that the intestinal tract should be considered an important source of vaginal yeast infection and reinfection. It might be necessary, if relapses are to be prevented, to treat not only the vagina but also the intestinal tract. In 2 women suffering from recurrent yeast vulvovaginitis we succeeded in preventing relapses by eliminating the yeasts from the intestinal tract by oral treatment with Chlorquinaldol. Trials in large series will be necessary, however, before conclusions can be drawn.

The urine as a possible source of vaginal yeast organisms was studied in a group of 124 unselected pregnant women. As can be seen from Table IV, of a total of 33 women with positive vaginal cultures 18 had yeast organisms in the vagina.

This high degree of correlation is even more impressive when Table V is studied. As shown in the first two columns, in all cases of simultaneous occurrence of yeast organisms in the vagina and urine the same species were involved. Do these findings prove that urine is a source of vaginal yeast infection? No, because it might be the other way around—yeast organisms may enter the urethra from an infected vagina. That the latter supposition is true can be seen from the last column of Table V. After elimination of the yeast from the vagina by local treatment it disappeared spontaneously from the urine in all cases. We cannot confirm, therefore, Magara's[2] opinion that urine is a source of any importance of vaginal yeast infection.

Our findings on yeast organisms in the feces and urine of women with vaginal yeast organisms suggest that in many cases of yeast vulvovaginitis or of simple occurrence of yeast organisms in the vagina the following mode of infection is at work: Certain yeast species like *C. albicans* or *T. glabrata,* potentially capable of vaginal invasion, may live habitually in the intestinal tract. By the anoperineal route a few cells enter regularly into the vulva and the distal part of the vagina. Normally these cells do not survive for a long time. When favorable conditions are found (which may occur, as is well known, in association with pregnancy, diabetes, treatment with wide-spectrum antibiotics, etc.) the cells may multiply and produce a yeast population in the vagina. Depending on the density of the yeast population as well as on the yeast species involved subjective and objective symptoms of yeast vulvovaginitis may or may not be produced.

In either case yeast cells enter regularly into the distal part of the urethra where they are not able to establish a population but are regularly washed down with the urine. Therefore, when yeasts are eliminated from the vagina the urine rapidly becomes

Table IV. Yeast organisms in the vagina and urine in 124 women

Vagina and urine both positive	18
Vagina positive, urine negative	15
Vagina negative, urine positive	2
Vagina and urine both negative	89

Table V. Influence of local vaginal treatment on yeast organisms in the urine in the 18 women who had yeast organisms simultaneously in the vagina and urine

		Urine	
No. cases	*Organisms found in the vagina*	*Simultaneous with first vaginal culture*	*One week after completion of local vaginal treatment*
13	*C. albicans*	All 13 *C. albicans*	All 13 negative
2	*C. albicans* and *T. glabrata*	Both *C. albicans* and *T. glabrata*	Both negative
2	*T. glabrata*	Both *T. glabrata*	Both negative
1	*C. krusei*	*C. krusei*	Negative

yeast-free. The regular invasion of the vulva and vagina from the anus continues, however, and relapses will occur as long as vaginal conditions prevail which are favorable to the growth of yeast organisms.

Two methods seem indicated to prevent these relapses: reversion of the vaginal conditions which favor infection or elimination of the yeast organisms from the intestinal tract.

Summary

Evidence is brought forward suggesting that (1) the intestinal tract is an important source of vaginal invasion by yeast organisms, and (2) the urine is normally not a source of vaginal invasion by these organisms.

We are much indebted to J. R. Geigy, Basel, Switzerland, for the free supply of Chlorquinaldol and to Sanitas, Lisbon, Portugal, for Trichomycin.

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Evaluation of some of the therapeutic mechanisms in the treatment of trichomonas vaginitis

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THE plethora of compounds available for the treatment of trichomonas vaginitis and the reports acclaiming the effectiveness of each of the widely varied substances lend credence to the assumption that the organism is sensitive to almost any protoplasmic toxin.[1] On the other hand, the vast number of patients seen, including those previously treated as well as those with a primary infestation, bears witness to the frequency of the inabilities of the drugs to do more than temporarily suppress the condition or, at best, to provide clinical and laboratory remission for varying periods of time.

Sufficient evidence is now at hand to support the belief that *Trichomonas vaginalis* is capable of completely reproducing the clinical vaginitis without the aid of symbionts or abnormal physiologic states of the vaginal membranes.[2, 3] There are also data to support the assumptions that emotional crises may induce exacerbations of a clinically quiescent infestation[4] and that spontaneous cure, possibly by virtue of the development of a resistance on the part of the host to the organism, is not frequent.

The present report is designed to demonstrate the frequency of clinical and laboratory remissions of infestations by *T. vaginalis* after treatment by a known potent trichomonicidal agent. Evaluation of the psychogenic element in nonspecific therapy and of the incidence with which spontaneous remission occurs during the time required to carry out the therapeutic process is attempted.

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Materials and methods

Two groups of patients were established. Group A comprised 50 patients, all of whom met the following criteria: white, married, nonpregnant, and premenopausal, and who gave no prior history of therapy for vaginitis of any type. These were permitted to participate in the testing of what they were told was a new therapy for vaginal irritation.

Group B was composed of 50 patients. These were white and nonpregnant, but were unrestricted as to age. Each had been treated one or more times previously for a vaginitis caused by infestation with *T. vaginalis* with a drug other than that under investigation.

The examination and treatment schedule was identical for all patients: following a routine history and physical examination, an inspection of the vagina was carried out with a speculum lubricated only with water. A sample of the vaginal contents was mixed with an equal amount of normal saline on a clean glass slide and immediately placed under the microscope.

Identification of motile flagellates was followed by the routine bimanual examination and a reinsertion of the speculum. The interior of the vagina was then thoroughly swabbed with one of the investigational solutions.

No patient was told to restrict her activities, sexual or otherwise. If it seemed likely that menstruation would interrupt the therapy, the patient was instructed to return one week following cessation of the bleeding when the treatment was begun with the initial swabbing of the vagina.

All 100 patients were re-examined one week, one month, and 3 months after completion of therapy.

The investigational material consisted of a vaginal solution and suppositories. The material used in the treatment of the 50 patients in Group A was coded so that the physician did not know whether he was using active therapeutic material or simply a placebo composed only of the vehicle in the swabbing solution or the base of the vaginal suppositories. Uncoded material was used in Group B.

The coded material for vaginal swabbing of Group A patients was either 1 per cent arsthinol in propylene glycol for vaginal surface application by cotton-tipped applicators, or the placebo solution, propylene glycol, alone. The coded vaginal suppositories contained either 50 mg. arsthinol in a specially blended base or the base alone. The size, shape, color, and consistency of these two types of suppositories were identical. The uncoded material used for the 50 patients of Group B consisted of the same therapeutic vaginal solution and suppositories except that in addition the solution contained 0.2 per cent hydrocortisone and each suppository 5 mg. hydrocortisone.

The code was revealed to the physician only after the 50 patients had been treated when the identity of the substance used was obtained and recorded on a specially prepared data sheet. Twenty-five patients received arsthinol, the others the placebo. The latter 25 constitute the basic control group of patients.

Since thorough vaginal swabbing constitutes an essential aspect of treatment with these preparations, we instructed each patient on her own use of the solution-soaked cotton-tipped application at home immediately preceding insertion of the vaginal suppository.

Results

In Group A it was found that 18 of the 25 patients (72 per cent) receiving arsthinol obtained both clinical and laboratory remission at the end of one week following discontinuance of the therapy (Table I). By the end of 3 months 12 per cent were again complaining of vaginal irritation and 20 per cent were found to have a laboratory recurrence of the infestation.

Eight (32 per cent) of the patients receiving the placebo obtained a remission of symptoms by the end of the first week, but only 3 patients (12 per cent) were found

Table I. Comparison of the incidence of clinical and laboratory remissions in patients receiving arsthinol (Group A) and arsthinol with hydrocortisone (Group B) with those (Control) receiving only placebo medication

	No. of patients	*Remission*				*Recurrence*			
		Clinical		*Laboratory*		*Clinical*		*Laboratory*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Group A.									
Drug	25	18	72	18	72	3	12	5	20
Control	25	8	32	3	12	5	20	5	20
Group B.									
Drug	50	46	92	42	84	8	16	8	16

to have no organisms in the slide. After 3 months 5 of the 8 patients had a recurrence of symptoms and all these 5 were found to again harbor the *T. vaginalis.*

In Group B, 46 patients (92 per cent) receiving the arsthinol and hydrocortisone combination became immediately asymptomatic, and, of these, 42 (84 per cent) were found to be free of the organism by the slide test one week following cessation of therapy.

At the end of 3 months 8 patients (16 per cent) were found to have both clinical and laboratory recurrence.

Comment

The value of specific trichomonocidal therapy in the care of the patient with an infestation by *T. vaginalis* is unquestioned. Most of the drugs in present-day usage will produce clinical remissions and parasite-free smears and/or cultures in all but a small percentage of those patients treated. Arsthinol and arsthinol with hydrocortisone were used in the present experiment because of their effectiveness and their ability to produce results within a short period of time.

Treatment by placebo medication was not ineffective; one third of the patients given a suppository that contained no trichomonocidal drug obtained a remission from pruritus and discharge. This concept fits in with the reports stressing the part played in the symptomatology by the emotions, and with the opinions of the patients themselves who notice that emotional crises precede each recrudescence of the disease.

It is of interest, however, that over 10 per cent of those patients who received inactive medication became free of the organisms. Here it is only possible to assume that an immune reaction has taken place within the vagina during the period of time that treatment was prescribed. This reaction could be used to account for the patients who lose their symptoms while awaiting an appointment to the physician and who appear finally with normal findings. Contrary to this, those patients who fail to respond to any or all drugs (or who remain asymptomatic only when under continuous therapy) may simply be those who are unable to produce resistance to the parasite.

The use of cortisone and related steroids as antipruritic agents is well known,[5, 6] and it may be that its inclusion in the vaginal therapy has served no other purpose. Its use in patients who have had recurrences or who have resisted other forms of therapy has seemed to produce a potentiation of the arsenical although the series is too small and the laboratory investigation too meager for clarification on this point.

Conclusions

The clinical symptomatology noted in vaginitis caused by *T. vaginalis* may be explained solely by the irritating effects of the parasitic infestation in most instances.

Emotional factors are important in some patients. Treatment with ineffective preparations may cause remission of symptoms despite a failure to free the vagina of the organism.

It would seem that the development of resistance to the parasite by the host is the most important factor in producing cure. The failure of the patient to produce immunity would explain the "resistant individual" and the high incidence of recurrence of vaginitis due to the *T. vaginalis.*

The supplies of arsthinol and arsthinol with hydrocortisone vaginal solution and suppositories were made available for this study by Dr. Edward A. Barrett, Medical Director, Endo Laboratories, Richmond Hill, New York.

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Hodgkin's sarcoma of the cervix

Report of a case

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SARCOMA of the cervix of either the localized or diffuse type is relatively uncommon, but Hodgkin's sarcoma primary in the cervix without involvement of lymph nodes or other organs is extremely rare. A review of the American literature reveals no case where Hodgkin's sarcoma is primary in the cervix as it apparently is in the case presented here.

Many histologic types of sarcoma are found in the uterus. Marcella and Keith[1] classify these sarcomas into three types—the spindle cell type, the round cell type, and the mixed cell type. The mixed cell type or mixed mesodermal sarcoma is variously called the mixed Müllerian tumor, carcinosarcoma, sacroma botryoides, or malignant mixed tumor or Müllerian origin.[2]

The mixed mesodermal tumor of the fundus of the uterus is the so-called mesodermal tumor which corresponds to the sarcoma botryoides found in the cervix. Hardy and Moragues[3] reported 116 cases of mixed tumors before 1950, and since then another 234 cases have been mentioned in the world's literature.[1]

Sarcoma botryoides, the grapelike sarcoma of the cervix, was described by Spiegelberg[4] as far back as 1879 under the designation "sarcoma colli uteri hydropicum papillare." From a clinical viewpoint, the most interesting feature of this disease is that, while it may occur in adults, it has often been noted in infants. McFarland[5] collected reports of 74 cases, all occurring in patients under 22 years of age.

Special forms of sarcomas of the uterus have been described but they are more of pathologic than clinical interest. The term "malignant lymphoma" is used to designate a group of malignant conditions that are usually associated with enlarged lymph nodes and may involve the reticuloendothelial organs. The simplified classification of the malignant lymphomas into giant-follicle type, lymphosarcoma (lymphoblastic and lymphocytic types), reticulum cell sarcoma, and Hodgkin's sarcoma is well accepted and serves as a basis for orientation.

In some cases of Hodgkin's disease the proliferation of the reticulum cells overshadows all other elements and there is formed a tumor with the morphologic characteristics of a reticulum cell sarcoma and with metastatic phenomena. The similarity is furthered by the occurrence in some cases of reticulum cell sarcoma of giant cells indistinguishable from those of the Reed-Sternberg type. The criteria to distinguish Hodgkin's sarcoma from a reticulum cell sarcoma are not rigidly set. It seems preferable to reserve the term "Hodgkin's sarcoma" for those cases in which there is some evidence of pre-existence of the more pleomorphic cell form.

Primary extranodal manifestations of malignant lymphomas are unusual. From existing medical literature it would appear that primary or secondary malignant lymphomatous involvement of the female genital tract is rarely encountered in the practice

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of gynecology. Johnson and Soule[6] reported 5 cases of lymphosarcoma involving the genital organs in which the presenting complaints of the patients were primarily gynecological. Only one of this group manifested involvement of both uterine cervix and endometrium by lymphosarcoma without clinical or laboratory evidence of generalized disease. The other 4 cases were limited to the fundus.

Epperson[7] reported a case of reticulum cell sarcoma of the uterus in a patient who complained of menometrorrhagia and pelvic pain. The uterus was enlarged and an ulcerative lesion was observed on the cervix, the tumor involving both fundus and cervix.

Walton[8] described 2 cases of malignant lymphomas of the uterus with gynecologic symptoms. The first was presumed to be primary in the endometrium. The second was a primary infiltration of the cervix considered to be a local manifestation of chronic aleukemic lymphocytic leukemia.

Stein[9] described a case in which chronic lymphatic leukemia presented as a neoplasm of the cervix with vaginal bleeding.

Infiltration of any organ in the body has been described in advanced cases of malignant lymphoma but the apparent limitation of the malignant lymphomas to the genital organs is very rare.

P. P., a 48-year-old white woman, gravida vi, para vi, was referred on Feb. 14, 1956, by an internist who had noted a severe erosion of the cervix on a routine physical examination. Otherwise, the complete physical examination was reported as being normal. The Papanicolaou smear taken by the internist was reported as negative, Class I. The patient had no pelvic symptoms other than occasional contact bleeding in recent months. The menses had been regular and normal. The initial pelvic examination revealed a normal vaginal outlet with no abnormalities of the Bartholin glands, Skene's glands, or vulva. The vagina was normal except for a stenosis of the upper third. Inspection of the cervix with a speculum revealed that only an area 2 cm. in diameter of cervix was visible and that this visible area of the portio vaginalis was severely eroded. A second Papanicolaou smear was taken which was reported as Class II, showing hyperplastic squamous cells and inflammatory exudate.

The patient was admitted to the hospital for further study of the cervix. Examination under anesthesia confirmed the findings of the pelvic examination. The adhesions of the vaginal wall to the portio of the cervix were dense; these adhesions were broken up with the examining finger and it was found that the cervix was actually rather large and there was a severe papillary erosion covering the entire portio. There was also a rough eroded appearance to the vaginal mucosa in the region of the vaginal fornices and there was considerable purulent exudate present in the vaginal fornices which was released after the adhesions of the vagina to the cervix were broken up. A sharp knife conization of the cervix was carried out. The bleeding was controlled with a Bovie electrode. A thorough fractional dilatation and curettage of the uterus was done. The endometrial tissue appeared grossly normal. The uterus was found to be slightly enlarged but symmetrical, and the uterine cavity was perfectly regular. The adnexal organs were normal, and there was no induration or fixation in either parametrial region or in the cul-de-sac. The conization specimen was thoroughly studied; the pathologic diagnosis was severe chronic inflammation of the cervix. It was noted in the microscopic description of the cervix that there was a rather marked infiltration with lymphocytes. Due to the fact that the gross appearance of this cervix had such a definite malignant appearance, the slides were shown to several pathologists, and all agreed that the specimen showed only chronic infection. The endometrium was normal in the proliferative phase. The patient was discharged from the hospital after an uneventful postoperative course.

She was seen on April 18, 1956. At that time, the cervix still showed a raw appearance and there was a recurrence of the adhesions of the vaginal walls to the side of the cervix. These adhesions were broken up with the examining finger. The patient was again seen on May 2, 1956. At this time, the cervix appeared fairly well epithelized and clean. The patient was seen again in June, 1956, and the cervix appeared normal with the portio vaginalis well epithelized. The patient was advised to return for regular check-ups every 3 to 6 months. However, she failed to follow this advice and she was not seen

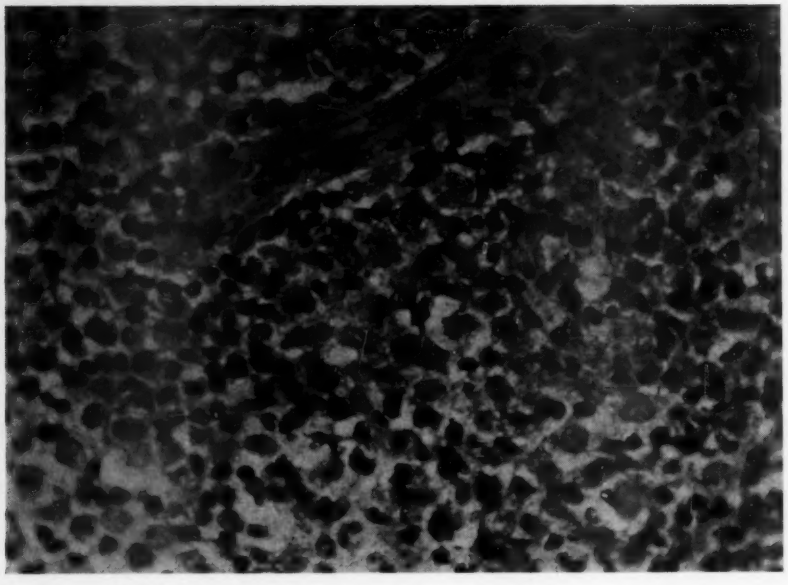

Fig. 1. Section shows an endocervical gland surrounded by relatively homogeneous cellular tumor tissue. (×30.)

again until February, 1959. At that time, the patient reported that she was having severe vaginal bleeding. Prior to this episode of bleeding, menstruation had continued to be perfectly normal and the patient had had no unusual symptoms and no intermenstrual bleeding. The episode of bleeding in February, 1959, was a prolongation of a normal period with definite hemorrhaging.

The patient was admitted to the hospital where findings on general physical examination were normal. Pelvic examination revealed the cervix to be identical to that described on the initial examination in 1956. Because of excessive bleeding from the cervix, the patient was given one unit of blood.

A repeat curettage and conization of the cervix were performed. At this time, examination under anesthesia revealed a recurrence of the adhesions of the vaginal wall to the cervix, so that only a small area of cervix, 1 cm. in diameter, was visible prior to separation of the adhesions. After separation of the adhesions the cervix was well visualized and was found to be large. There were large, fatty papillary projections from the entire portio vaginalis, and the cervix bled freely. The cervix was so friable that large pieces of this fatty tissue could be removed from the cervix with ring forceps. The uterine cavity was found to be slightly enlarged; the curettings appeared normal with no evidence of the sarcomatous tissue within the uterine cavity. A vaginal pack was inserted to control the bleeding from the cervix.

The biopsy specimen from the cervix at this time was reported as showing sarcoma, Hodgkin's type. The pathology report showed that there was a complete replacement of endocervical stroma by sheets of malignant reticulum cells with a pleomorphic infiltrate, and typical Reed-Sternberg cells were present. The cells showed rather marked nuclear variation and were hyperchromatic with some loss of cohesiveness. A few residual cervical glands identified the tissue. These appeared cystically dilated and filled with inspissated secretion. Section from the endometrium showed moderate glandular hyperplasia with edema of the stroma. The diagnosis was Hodgkin's sarcoma in lymphosarcomatous base (lymphoblastic) (Fig. 1).

In view of this diagnosis, an internist was called in consultation to evaluate the patient's condition. A complete physical examination was done by the internist and was reported as showing no abnormality. There was no palpable lymphadenopathy present. The spleen and liver were not considered to be enlarged. The heart and lungs were normal to examination. A chest x-ray film was reported as normal. There was no widening of the mediastinum. Roentgen examination of the gastrointestinal tract was negative except for a small hiatus hernia. Intravenous urograms were reported as normal. A barium enema was reported as normal. Laboratory findings revealed an erythrocyte count of 3.41 million, hemaglobin level 10.5 Gm. per cent, and a leukocyte count 5,600. The differential count revealed 65 per cent segmented

neutrophils, 2 per cent bands, 34 per cent lymphocytes, 1 per cent monocytes. Blood urea nitrogen level was 13.2 mg. per cent and the fasting blood sugar level was 132 mg. per cent. Sigmoidoscopy was performed and revealed no abnormal findings of the rectum or rectosigmoid. Cystoscopic studies were performed and the bladder was found to be normal.

The course of treatment elected was pelvic radiation. The patient was given 5,000 r in separate doses on anteroposterior direction. She was seen and examined on March 13, 1959, having had 8 cobalt therapy treatments. At this time the cervix was normal except for hyperemia. No erosion of the cervix was present. The patient was again seen on April 9, 1959, after having completed the cobalt radiation therapy. At this time the cervix showed a very slight erosion and some scarring in the vaginal fornices.

The patient was readmitted to the hospital on April 19, 1959, for completion of the radiation therapy by means of radium. On April 29, an Ernst applicator was inserted containing 70 mg. of radium (30 mg. in tandem and 20 mg. in each arm of the Ernst applicator). The Ernst applicator was left in place for 24 hours, giving a dosage from the radium as follows: 6,336 r to the cervix, 1,512 r to Point A, and 456 r to the Point B. This combined with the radiation dosage to make a total of 13,304 r given to the cervix, which covers the therapeutic dose (12,000 r) for Hodgkin's sarcoma of the cervix.

A biopsy showed a fibrous stroma diffusely infiltrated by lymphocytes and neutrophils with numerous tiny blood spaces lined by a single layer of endothelial cells. There was no specificity to the inflammatory reaction, but the vascularization suggested radiation reaction. The endometrium showed marked epithelial hyperplasia with nuclear enlargement, hyperchromatism, and variation with retention of glandular outline. This was also ascribed to radiation effect.

Blood was found to be normal, and smears of bone marrow showed a liberal admixture of peripheral blood. Progression could be traced in the myeloid series and appeared normal. The erythroid series was represented by very few forms in the smears. Sections of the clot failed to show any bits of marrow.

The general condition of the patient was at all times good. She tolerated all the radiation therapy well with only slight diarrhea.

Summary

A case of Hodgkin's sarcoma of the cervix has been presented without clinical or laboratory evidence of generalized manifestation of the disease. The differentiation between the various types of sarcoma is sometimes very difficult because by the time the patient is seen, the origin of the cell type is often obscure. Most often, surgical treatment for sarcoma of the uterus would be the first choice. In this case, however, radiation was used because Hodgkin's sarcoma is most often a generalized disease, rarely a localized one. For the present, it is felt that the treatment given has controlled the only site of the disease that was apparent at this time. The patient has left the hospital, and her progress will be followed closely.

I wish to express thanks to Dr. David Leavenworth for his permission to use the case presented in this article.

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Adenocarcinoma of the paraurethral glands

Report of a case

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PRIMARY malignant tumors of the female urethra are of infrequent occurrence. McCrea,[7] in an extensive review of the literature in 1952, found 546 authenticated cases. Of this group, 504 were carcinomas, 23 sarcomas, and 19 were melanomas. Of the 504 carcinomas, only 48 were adenocarcinomas originating in the paraurethral glands. McCrea concluded that this malignant disease, although rare, is more frequently found in the female than in the male. He also reported that treatment over the years has been unsatisfactory.

Graves and Guiss[5] in 1941 at Pondville Hospital, which is devoted entirely to the care of neoplastic diseases, reviewed all urethral carcinomas seen during the preceding 14 years. There had been only 10 cases of cancer of the female urethra during that period. Two of these cases were found to originate in the paraurethral glands.

In 1955 Fagan and Hertig[4] reported 8 cases of carcinoma of the female urethra at the Free Hospital for Women from 1935 through 1954. All were of squamous or transitional cell type.

The most recent report is that by Brack and Dickson,[2] who discuss 14 additional cases. Eight were of the vulvourethral type and 6 were of the urethra. Eleven were diagnosed microscopically as epidermoid carcinoma, one as urethral caruncle with malignant degeneration, one as carcinoma in a polyp, and one as lymphosarcoma.

Because of its rarity, the present case of an adenocarcinoma originating in the paraurethral glands is reported.

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R. S., a 61-year-old white woman, was seen in the Touro Infirmary Out-Patient Department on July 25, 1958, with the complaint of having recently noted small amounts of bright red blood on the tissue paper after voiding. There were no associated symptoms of pain, pruritus, or discharge. She was referred to the Gynecology Clinic.

Past history. She gave a past history of having had a subtotal hysterectomy performed at another hospital in 1947. She voluntarily was examined at the Hutchinson Memorial Cancer Detection Clinic on Feb. 28, 1949. Pelvic examination at that time showed an area of leukoplakia involving the anterior vestibule between the clitoris and the urethral meatus. Papanicolaou smears were reported as negative for malignant cells. In 1955 the retained cervical stump was removed and a cystocele and rectocele were repaired. Examination at that time revealed moderately advanced arteriosclerotic cardiovascular disease with cardiac enlargement. She also had a history of diabetes mellitus and psychiatric treatment for mental depression for many years.

Examination. Examination of the patient in the clinic on July 28, 1958, revealed a 0.5 by 0.25 cm. grayish pink, friable, fungating lesion of the anterior vestibule approximately half way between the clitoris and the urethral meatus. A biopsy specimen of the mass was secured. Microscopically, the tissue changes were suggestive of metastatic adenocarcinoma. Because of the smallness of the biopsy specimen, more tissue was requested.

First hospital admission. The patient was admitted to the gynecologic ward service on Aug. 4, 1958. A relatively wide excision of the lesion was performed.

Microscopic description of vulvar biopsy. Sections showed a circumscribed neoplasm located primarily in the dermis and having a cystic and, in some areas, papillary architecture. It was composed of columnar or transitional type cells in a pseudostratified arrangement. In areas there was abundant mucus production. The cells showed moderate pleomorphism and mitotic figures were fairly numerous.

This neoplastic epithelium extended upward to involve the overlying squamous epithelium to the surface. This was thought to represent the tract of the original duct replaced by neoplasm.

Adjacent to the neoplasm a duct coursed through the dermis to open through the squamous epithelium on the surface. This structure was lined by a stratified transitional epithelium within which small pseudoacini occasionally were formed. This tubular gland was of the paraurethral type and the neoplasm described was thought to originate from a gland of this type.

Adenocarcinoma of paraurethral glandular origin was the tentative microscopic diagnosis. A complete study to determine extent of spread of the disease was then undertaken.

Laboratory data. Routine laboratory results, including complete blood count, fasting blood sugar level, nonprotein nitrogen level, urinalysis, and phenolsulfonphthalein level, were within normal limits. Gastric analysis was normal. Chest x-ray examination showed a considerably enlarged cardiac shadow compatible with advanced arteriosclerotic cardiovascular disease. A skeletal survey was negative for metastatic involvement. Proctoscopy, sigmoidoscopy, and barium enema with air contrast showed no evidence of intrinsic pathologic conditions in the colon. The gastrointestinal series showed a small esophageal hiatal hernia and hypertrophic gastritis. An electrocardiogram was within normal limits. Genitourinary work-up including, intravenous pyelogram, retrograde pyelogram, and panendoscopy, was normal.

Following work-up the microscopic sections were reviewed by the Pathology Departments of Touro Infirmary and Tulane University School of Medicine. The diagnosis of adenocarcinoma of the paraurethral glands was made unanimously (Fig. 1). Because of the malignant nature of this lesion, it was decided to go ahead with an extensive vulvectomy and bilateral Basset type node dissection. The patient, however, refused surgical treatment at this time so that she could attend to personal matters.

Second hospital admission. On Sept. 16, 1958, the patient was readmitted. An extensive vulvectomy and partial urethrectomy were per-

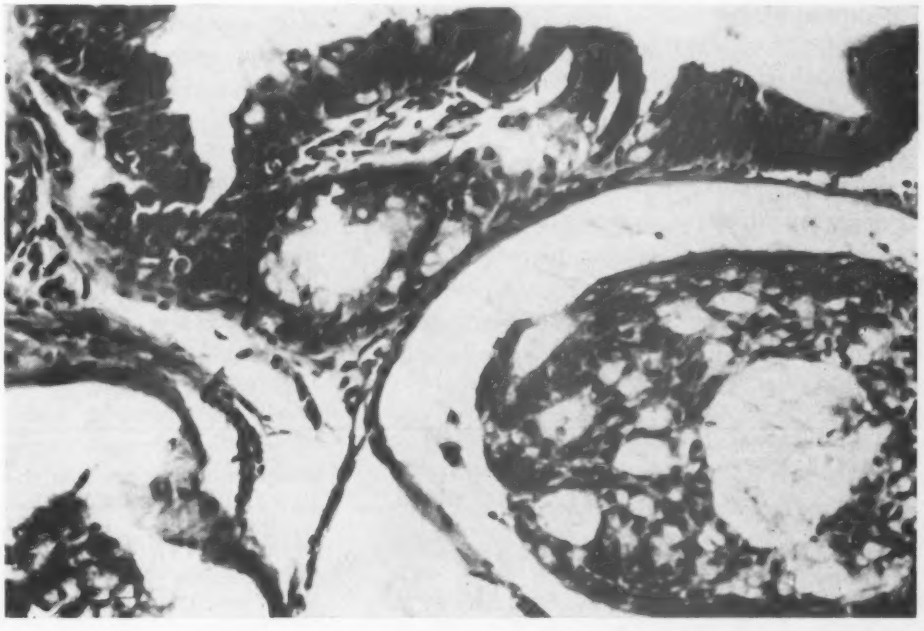

Fig. 1. Microscopic section of the vulvar biopsy specimen shows a circumscribed neoplasm located primarily in the dermis and having a cystic and, in some areas, papillary architecture. It is composed of columnar or transitional type cells in a pseudostratified arrangement. In areas there is abundant mucus. The cells show moderate pleomorphism, and mitotic figures are fairly numerous.

formed on Sept. 18, 1958. The bilateral Basset inguinal and femoral node dissections were carried out one week later. Pathology reports revealed no residual carcinoma. The distal segment of the urethra showed no premalignant or malignant changes. All removed nodes were negative for metastatic carcinoma. The postoperative course following these extensive procedures was essentially benign except for slough of the groin dissections.

She was last seen in the Out-Patient Clinic in March, 1959, and was found to be doing well. She was working 2 days a week.

Comment

Adenocarcinoma of the female urethra makes up one of the smaller groups of malignant tumors. Most of the carcinomas have been squamous carcinomas. A still rarer type of mucoid carcinoma has been reported by Menville and Counseller.[8]

According to Walker and Huffman,[9] the adenocarcinomas have their site of origin in the paraurethral ducts and glands. This was proved to be true in this case.

The important factor in any case of urethral carcinoma is the method of treatment.

Everett[3] cites the 2 small series of cases of Fagan and Hertig and of Brack and Dickson in which the best results were obtained with irradiation. He, therefore, recommends this as the treatment of choice for this type of tumor.

Auer[1] has stated that he does not regard deep x-ray therapy as an effective agent locally or for the glandular metastases. He believes that the absence of gross involvement and even the small size of the tumor should not encourage conservatism as regards the groins.

The British[6] recommend that if the growth is confined to the lower urethra it can be excised together with the anterior part of the vulva and the superficial and deep inguinal glands on both sides. Alternatively, or as an adjunct to operation, radium needles can be implanted around the urethra so as to irradiate the growth with the calculated dose. The regional lymph glands can then be excised on each side. If the growth is more extensive when first seen, reliance must be placed upon radiotherapy alone or a very extensive operation must be undertaken.

It was our feeling in this case, and it seems to be true in many cases, that these tumors, through their position at or near the urethral meatus, share in the more superficial drainage of the vulva to the nodes of the inguinal regions. This is certainly true with respect to carcinoma of the vulva in general, in which spread is directly to the superficial inguinal and subinguinal groups of nodes and from there to the nodes of Cloquet and then to the external iliac nodes.[10] Therefore, any procedure less than that performed here would have been entirely inadequate. It is true that all removed nodes were negative for metastatic carcinoma, but it is impossible to determine early metastasis to the groins before the nodes are large enough to be palpated.

Summary

A case of adenocarcinoma of the urethra originating in the paraurethral glands is reported. A method of therapy has been outlined. Review of the literature shows the rarity of the lesion in which only 50 cases have been reported.

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Three genital tumors in one woman

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THE association of endometrial carcinoma with feminizing tumors of the ovary has been reported by various investigators. Dockerty and Mussey[3] found that 27 per cent of postmenopausal women with feminizing tumors also had endometrial carcinoma. Mansell and Hertig[11] came across endometrial carcinoma in 15 per cent of cases of granulosa–theca cell tumors. Ingram and Novak,[9] in a review of literature on this subject from 1920 to 1949, collected 50 cases and added 4 of their own. A recent review of Greene[6] has brought the figure to a total of 132 cases. This frequent association appears beyond the law of chance. To the best of our knowledge, however, we do not know of any reported case of feminizing mesenchymoma of ovary and carcinoma of endometrium associated with carcinoma of cervix. A case of such a combination of 3 genital tumors in one individual is reported below.

Case report

A 40-year-old Hindu woman was admitted on Dec. 13, 1955, because of irregular profuse vaginal bleeding of 10 years' duration. Before this, the periods were regular, occurring once in 30 days and lasting for 4 to 5 days. For the preceding 10 years the periods were irregular, occurring once in 3 to 6 months and lasting for nearly 2 months. The bleeding was painless and profuse with the passage of clots. She was married but had never been pregnant. On physical examination a tumor, 4 by 4 inches, was palpated in the right iliac fossa. It was freely mobile. No free fluid was present in the peritoneal cavity. The uterus was found to be enlarged to the size of a 12 weeks' gestation, firm and mobile. A firm tumor, 4 by 4 inches in size, continuous with the one felt per abdomen, was palpable high up in the right fornix. The left fornix was free. Speculum examination showed the cervix to be healthy; there was slight blood-stained vaginal discharge. A panhysterectomy was done.

Gross description of specimen. The colpocervix was unremarkable. The external os was patulous. The entire endocervical canal was occupied by an endophytic tumor which had infiltrated the wall of the cervix. A large papillary tumor mass, 4 by 3 cm., occupied the fundal portion of the uterine cavity. It was soft, friable, and pinkish gray. The right ovary measured 10 by 12 by 8 cm. Its external surface was smooth and glistening. The sectioned surface was more or less solid except for a few cystic areas. The solid portion was soft, pale yellow, and necrotic. The left ovary was normal.

Microscopic description. The ovarian tumor was made up almost entirely of granulosa cells in large clumps separated by fibrous trabeculae (Fig. 1). The cells showed prominent nuclei with absence of mitotic activity. There was a general lack of folliculoid pattern except in some fields where pseudoadenomatous pattern of granulosa cells was seen. Intermixed were plump, fusiform cells characteristic of thecal stroma. Some of the granulosa cells also showed luteinization.

The tumor from the body of the uterus was

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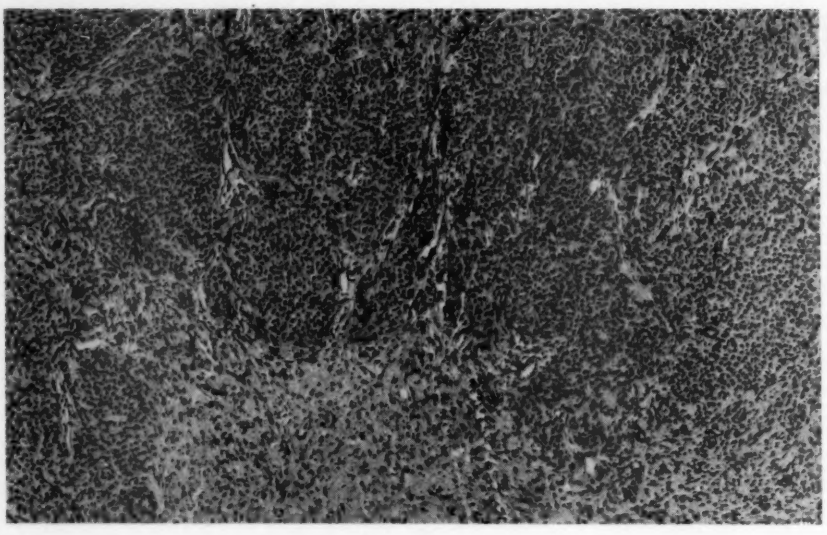

Fig. 1. Granulosa–theca cell tumor of the ovary.

glandular, showing great disparity in gland size, shape, and pattern. Most of the glands showed back-to-back arrangement (Fig. 2) and were lined by epithelial cells with all the features of malignancy and extensive metaplastic changes. There were sheets of squamous epithelial cells showing prickles. These metaplastic epithelial cell masses were seen growing within the gland lumina. No feature of malignancy was noticed in the squamous element.

The cervical tumor was a moderately undifferentiated squamous carcinoma infiltrating

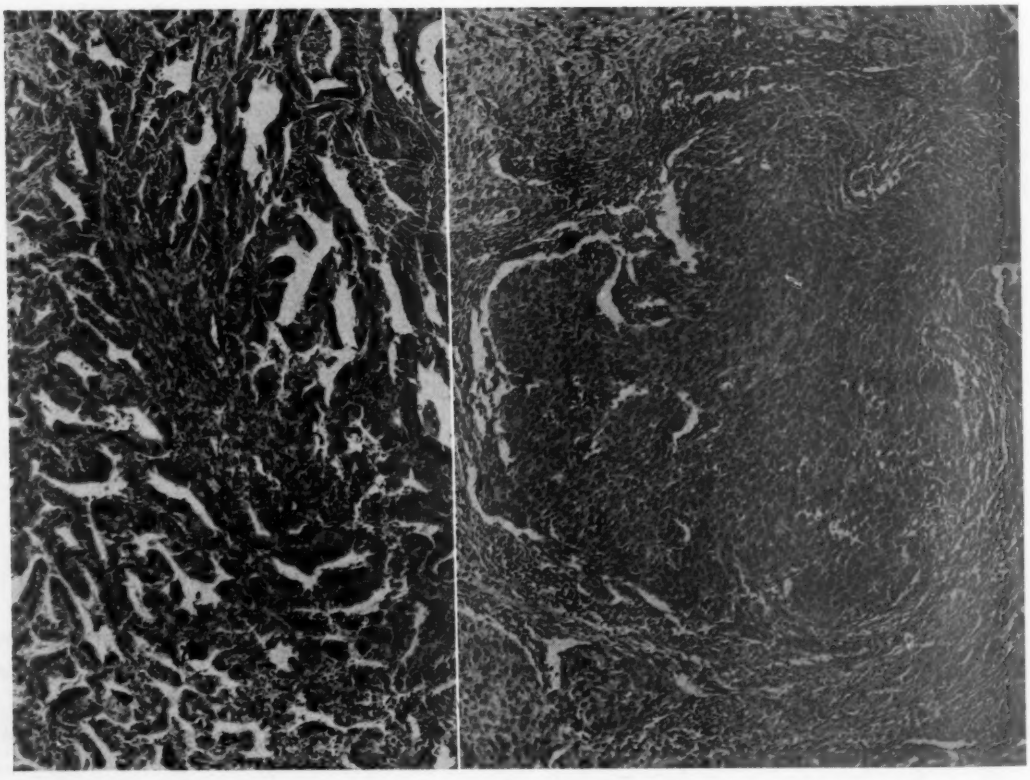

Fig. 2. Endometrial adenocarcinoma.

Fig. 3. Squamous cell carcinoma of the cervix.

Table I. Cases of feminizing tumors of the ovary associated with adenoacanthoma of the endometrium or carcinoma of the cervix or both

Author	*Year*	*Ovary*	*Uterus (endometrium)*	*Cervix*	*No. of cases*	*Comment*
Hodgson, Dockerty, and Mussey[8]	1945	Thecoma	Adenoacanthoma	No change	1	Report of 62 granulosa cell tumors
Grey[7]	1950	Granulosa	Adenoacanthoma	No change	1	Case report
Ingram and Novak[9]	1951	Granulosa	Adenoacanthoma	Squamous metaplasia	1	4 cases of combined tumor
Banner and Dockerty[1]	1945	Thecoma Thecoma	No change No change	Epithelioma Adenocarcinoma	1 1	Report of 23 cases
Kothare and Andrews[10]	1957	Granulosa	No change	Epithelioma	1	Case report
Present case	1958	Granulosa	Adenoacanthoma	Epithelioma	1	Case report

the wall of the cervix (Fig. 3). In one of the sections, small remnants of carcinoma in situ were seen on the surface.

Final diagnoses.

1. Granulosa cell tumor of the right ovary with some luteinization and some thecal stroma.
2. Adenoacanthoma of the endometrium.
3. Undifferentiated squamous cell carcinoma of the cervix.

Comment

Schroeder,[12] in 1922, was the first to report the association of a granulosa cell tumor of the ovary and endometrial adenocarcinoma. Out of 66 consecutive cases of feminizing tumors of the ovary observed in the laboratory of gynecologic pathology of the Johns Hopkins Hospital, in only 4 instances were these tumors associated with endometrial carcinoma.[9] Dockerty and Mussey,[3] who studied 87 mesenchymomas of the ovary encountered at the Mayo Clinic, found associated uterine carcinoma in 15 instances; in 3 of these cases there were, in addition, cancers of the breast. Greene[6] has reviewed the literature since 1949 and has collected an additional 67 cases. The Ovarian Tumor Registry of the American Gynecological Society included 13 instances of such combination.[6]

This frequent association of feminizing tumor of the ovary with endometrial carcinoma suggests a possible predisposing role of these tumors in the production of endometrial carcinoma. Schuschania[13] demonstrated an increased amount of urinary estrogen and estrogen in the tumor tissue and established that the granulosa cell tumor produces this hormone. It has been shown experimentally that administration of exogenous estrogen produces endometrial hyperplasia in the laboratory animal. Mansell and Hertig[11] have observed an abnormally stimulated endometrium in 60 per cent of cases of granulosa–theca cell tumor. Fremont-Smith and associates[4] have reported a case of endometrial carcinoma developing in a woman who accidentally had received large doses of estrogen extending over a period of 8 years. In spite of this experimental as well as clinical evidence, whether or not estrogen can incite the development of endometrial carcinoma is still a moot question.

Ingram and Novak's[9] study of reported cases of combined tumors in the literature included 28 thecomas and 22 granulosa cell tumors. Greene's[6] review included 31 thecomas, 2 granulosa–theca cell tumors, and 24 granulosa cell tumors. This frequent association of thecomas with endometrial carcinoma as compared to granulosa cell tumors is striking. In general, the thecoma is a rarer tumor than the granulosa cell tumor. In the first 500 cases of the Ovarian Tumor Registry, only 6 thecomas were encountered, as compared to 67 granulosa

cell tumors. This supports the view that theca rather than granulosa cells are the sources of estrogen. The steroidal substances have been demonstrated only in the thecal tissue. Biskind[2] believed that the estrogenic effect of granulosa cell tumors is due to the varying admixtures of thecal elements in the tumors. The thecal stroma in the present case report accounts for the functional activity of the tumor.

The association of feminizing tumors of the ovary and cervical carcinoma is rare. Banner and Dockerty[1] have reported only 2 cases of such combination. Recently Kothare and Andrews[10] have added another case (Table I). Squamous metaplasia of the cervix was found in 2 of the 4 cases of feminizing tumor of the ovary and carcinoma of endometrium reported by Ingram and Novak.[9] Stohr[14] found this lesion in 2 of 3 cases. These cervical changes are considered a response to hyperestrogenism. Though experimentally Gardner and his co-workers[5] have induced carcinoma-like lesions in the cervices of mice receiving estrogen, squamous metaplasia of the cervix in women has not been conclusively proved to be a response to hyperestrogenism. In the present case, the cervical tumor appears to be unrelated to the ovarian tumor.

As compared to adenocarcinoma, the association of adenoacanthoma with a feminizing ovarian tumor is extremely rare. A search through the literature revealed only 3 cases of such combination (Table I).

Summary

1. A case of 3 genital tumors, with a combination of granulosa cell tumor of the ovary, adenoacanthoma of the endometrium, and epithelioma of the cervix, has been reported for the first time.

2. The available literature on this subject has been reviewed in brief.

We wish to express our thanks to Prof. A. T. Hertig, M.D., of the Free Hospital for Women, Boston, for the photomicrographs and for his opinion on the slides. Our thanks are also due Dr. Anjaneyulu, Reader in Obstetrics and Gynaecology, Medical College, Nagpur, for the clinical data.

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Mixed mesodermal tumors of the uterus

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A TEN year study of sarcoma of the uterus, taken from the records of the Sinai Hospital, has been reviewed and reported recently.[19] Since that time 3 unusual cases (one at The Hospital for the Women of Maryland and 2 at the Sinai Hospital) have been encountered. The microscopic examination of the specimen removed at operation revealed in each instance some of the characteristics of a malignant connective tissue tumor. However, there were elements found in 2 of the cases which were pathognomonic of those observed in a mixed mesodermal neoplasm. The remaining specimen was classified as an atypical fibromyxosarcoma.

Because of the interesting case histories, physical, operative, and pathological findings, and the subsequent postoperative course, it is felt that presentation of these case reports might contribute to the subject of sarcoma of the uterus, as well as add to the knowledge of mixed mesodermal tumors of the genital tract. The entire macroscopic and microscopic picture in our patients will be given in detail under the individual case reports. The tumors were categorized individually by the pathologists as (1) mixed mesodermal tumor, (2) osteogenic sarcoma, and (3) fibromyxosarcoma.

In a more thorough investigation of our cases and the reports of other bizarre varieties of tumors of the uterus, we found it hard to differentiate between the unusual sarcoma and the mixed mesodermal tumor. Often the diagnosis was equivocal even though it was made by a competent pathologist. In many instances a tumor is named according to its predominant element of heterologous tissue. McFarland,[14] after an extended study of mixed tumors of the urogenital region, expressed the idea that it was difficult for him to agree that the presence of any given heterologous component in a tumor should be accorded the undue prominence of lending its name to the new growth. With these thoughts in mind, a survey of some of the pathological features and a review of the histogenesis of mixed tumors might help to elucidate this perplexing differential in diagnosis. It is apparent from the recent literature that all opinions are not in accord.[5-10, 12-15, 17, 18, 21, 23] A correct diagnosis is not only important from the academic standpoint but is significant in its clinical application.

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Pathology

From the aspect of the pathology, a mixed mesodermal tumor is composed of a variety of types of mesodermal tissues.[1] They are thought to arise from mesenchymal tissue representing one germ layer.[6, 9] This is in contrast to the teratomatous lesion that arises from three germ layers and the dermoid tumor that arises from two. Whatever the causative factors, be they accidents of development, metaplasia, or the rejuvenation of "rests" of tissue, mixed tumors with a malignant potential have been known to appear in various parts of the body other than the female genitals. Some of the sites are the kidney, breast, salivary gland, bone, gastrointestinal tract, and skin.[22] Horn and Enterline[10] studied and classified 39 cases of

rhabdomyosarcoma found in numerous parts of the body. Their report confined itself to one type of mixed tumor.

McFarland[14] was able to find 119 different names in the literature prior to 1900 when these neoplasms were described. He preferred to use the term "dysontogenic" in describing mixed tumors. In this way he was able to include growths that appeared as simple single tissue tumors, as well as those that were composed of a variety of tissues. Although promulgated by so distinguished an investigator and astute observer, the term has not persisted. In the present-day literature these tumors are still referred to as "sarcoma botyroides"[16] when presenting the typical grapelike appearance or the more general and mystifying term of "mixed mesodermal tumor" is used.

Recently Ober and Tovell[18] proposed the term "mesenchymal sarcoma" in their descriptions of this neoplasm. This seems to be more logical since it denotes the origin plus the evidence of malignancy in its associated connective tissue components. Whatever the name, one of the two features is found in common in all of these tumors. Either they are polypoid in appearance or they have a predominant cell type. In addition to these characteristics, the tumors should be divided into two types. There is the simple one composed of one heterologous or homologous type of tissue.[6] In the complex variety multiple complexities of tissues are present. Here we approach an area of controversy. Marcella and Cromer[13] feel that in order for a new growth to qualify as a mixed mesodermal tumor, the neoplasm should be composed of 2 or more heterologous elements. Ehrlich[5] is more precise; he feels that the only tumors that can be classified as mixed mesodermal are those containing myoblasts with one or more other heterotopic elements present. These restricted views, however, are not generally accepted.

Incidence

No matter what type of classification is used, even in the broadest sense, mixed mesodermal tumors are rare in appearance. In 1941 Liebow and Tennant[12] presented their study of 65 such cases of the body of the uterus that they found in the literature. In the same year Glass and Goldsmith[7] found 95 patients with this diagnosis. Their cases included tumors of the cervix as well as of the body of the uterus. Ehrlich[5] in 1942 reported his findings in 12 cases, eliminating all the others since they did not meet with his criteria. Again in 1942 Schmidt and Schutz[21] reviewed this subject and added 2 of their own cases. By 1952, Hardy and Moragues[8] collected 118 cases up to the date of their report. The most recent studies have been by Ober and Tovell,[18] and Marcella and Cromer.[13] Up to the present time 234 cases have been reported in the world literature.[13] Although the rarity of occurrence is confirmed, we are convinced that many such malignancies have been encountered but have gone unrecognized and unreported. Laurain and Monroe[11] report a case of mixed mesodermal tumor associated with bilateral thecoma.

Location

While all of the tumors are similar in structure, they fall into three distinct groups according to location. In early childhood they may be found to originate in the vagina. During the active sex life they are found to arise from the cervix. In the menopause, the usual site is the body of the uterus. These facts are substantiated by Glass and Goldsmith[7] as well as Marcella and Cromer,[13] and Herbut.[9] There have been times when the cervical growth was observed in women in the menopause. Likewise the corporeal growth may be found in women during their active menstrual life. There is no relationship to parity since they are present in parous and nonparous women, in equal numbers.

Histogenesis

The origin and development of mixed mesodermal tumors has long been a debatable topic. Most authors support Wilms's theory of displaced embryonal germ tissue.

It is conjectured that the cells forming the tumor originate in the embryo and are incorporated into the anlage from which a structure is formed. This is in contradistinction to the theory that they are displaced and carried along with it. Willis[23] contends that "it is not logical to suppose that undifferentiated 'rests' of heterotopic tissue could remain in the endometrium for the whole childbearing period and then suddenly produce an unusual tumor." He supports the newer concept of the process of dedifferentiation and rejuvenation of the stroma of the mucosa. Further, he feels that the stroma is a peculiar and highly labile tissue which possesses wide potential for aberrant differentiation. Nicholson[15] feels that the origin and behavior of a tumor is to be found in terms of an abnormal response of tissue to a stimulus. This response conforms to certain relationships between the stimulus and the tissue and the tissue and the host.

The stimulation for the production of a new growth is unknown. Some think that it might be hormonal. Scheffey, Levinson, Herbut, Hepler, and Gilmore[20] report the development of an osteosarcoma of the uterus that had previously been irradiated for menorrhagia. This may be illustrative of the stimulus needed to produce a mixed mesodermal tumor, even though the authors have not labeled their cases as such.

In consideration of the facts concerning the pathology and the various theories offered in the development of mixed mesodermal tumors, it seems possible that 2 of the cases in our report may fall within this category. The third case has not been designated as this type of new growth, yet is a most unusually acting sarcoma. The variability of action even in a usual sarcoma has been noted previously by us[19] and others.[4] There is little security to be felt in regard to recurrence despite apparent encapsulation of the tumor. From our experience, the prognosis should always be guarded.

Sarcoma is found in 3 to 5 per cent[16] of all malignant neoplasms of the female genitals while the incidence of mixed mesodermal tumors is from 0.04 to 0.08 per cent.[18] The ability to differentiate between the two has been difficult on occasion. With a more thorough search of the microscopic sections of sarcomatous lesions it is possible that the incidence of mixed mesodermal tumors might show an increase.

Case reports

Case 1. Mrs. B. G., aged 53, was seen 2 to 3 months after the onset of vaginal bleeding. She had not had a menstrual period for 2 years prior to this episode. She had been examined about four years previously, at which time it was determined that she had a nonspecific pelvic inflammatory disease. With bed rest and antibiotic therapy she made an uneventful recovery. She was not seen again until the onset of the present illness. Menses had always been regular; they began at the age of 17, appeared every 21 days, and lasted 5 days. The last regular period occurred 2 years prior to the present illness. There had been one pregnancy 18 years previously that ended in cesarean section after a trial labor. The patient had no complaints referable to any of the other systems, and she had enjoyed good health up to the time she sought medical advice.

The physical examination revealed a well-developed, well-nourished white woman not in acute distress. There were no abnormalities elicited upon general somatic examination. However, the pelvic findings were of interest. The vagina was filled with a friable bleeding mass which could be palpated and seen just beyond the introitus. This seemed to be concomitant with a mass felt in the anterior portion of the corpus of the uterus. A re-examination under anesthesia was still unsatisfactory. Since the cervical os could not be delineated, a laparotomy was decided upon. At operation the uterus, tubes, and ovaries were easily removed. In order to excise the entire growth the vagina had to be entered posteriorly and the mass previously felt was shelled piecemeal through this incision.

After an uncomplicated postoperative course the patient was discharged from the hospital. Two weeks later she again complained of vaginal bleeding. A speculum examination of the vagina revealed a recurrent bleeding mass arising from the forniceal cuff, high in the vagina. She was brought to the hospital to have the mass removed. The microscopic examination

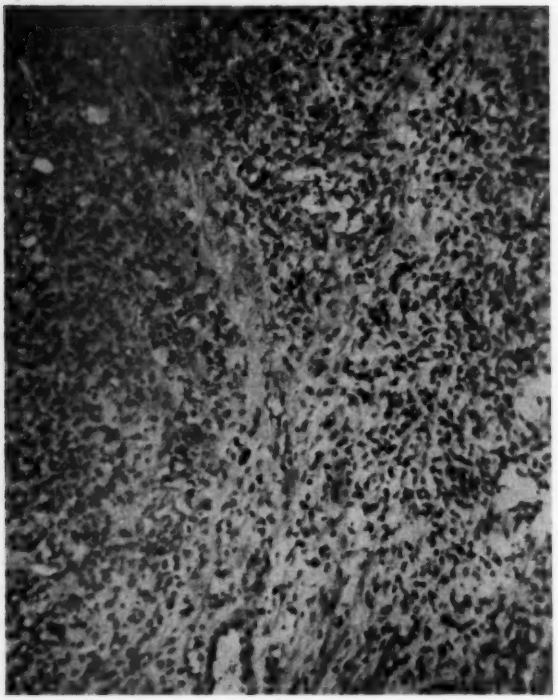

Fig. 1. Case 1. Low-power photomicrograph.

revealed the same type of fibromyxosarcoma found in the original pathology specimen. Radiotherapy was then instituted. Four ports were used, giving 3,600 r to each with a maximum center dose of 5,000 r.

The patient's condition became progressively worse. She became weak, was bedridden, had marked nausea and vomiting, could not eat, and began to lose weight. Because of her distress and inability to make any progress toward recovery and because of an increased evidence of ascites, she came into the hospital again. A paracentesis drained 4,000 c.c. of serosanguineous fluid from the abdomen. This fluid continued to re-form and drain through a retention catheter. There were now hard masses felt in both breasts and in the lower abdominal wall. An x-ray examination of the chest revealed a metastatic lesion in the base of the left lung. The red blood count and hemoglobin level dropped constantly. Repeated transfusions and replacement of electrolytes and fluids failed to make any change in the patient's condition and she died 8 months following the original operation. An autopsy was not permitted.

Pathology report.

GROSS. The specimen submitted consisted of a resected uterine fundus measuring 4.0 by 4.5 by 3.0 cm. which on gross examination showed no abnormalities.

The resected cervix and endocervical canal were submitted in multiple fragments, 20 in number, the largest of which measured 3.0 by 4.0 by 1.5 cm. All of this tissue was relatively homogeneous, with a pearl-gray color and the consistency of fibrous fatty tissue.

MICROSCOPIC. Section from the friable cervical tissue showed a uniform picture of a poorly encapsulated tumor composed of elongated spindle cells of varying size and shape. Many of the cells showed enlarged hyperchromatic nuclei with marked variation in the size of the nuclei. Many nuclei exhibited mitotic figures. A few of the spindle cells showed multiple nuclei. The stroma of the tumor in all areas was scanty and there were numerous thin-walled blood vessels. At the periphery of the tumor the muscle of the cervix showed invasion by the tumor.

The specimen consisted of 2 pieces of gray, soft, hemorrhagic tissue, measuring 3.5 by 3.0 by 2.5 cm. and 3.0 by 2.0 by 1.5 cm., respectively. The tissue on section was opaque and friable.

Microscopically there was a marked cellular tumor with many areas of necrosis and hemorrhage. In the main body of the tumor the cellular pattern was similar to that previously described with the exception that there were more nuclear irregularities and a greater number of cells with multiple hyperchromatic nuclei. At the periphery of the tumor there was a myxomatous stroma with relatively wide separation of the tumor cells. In these areas the cells exhibited a high nuclear cytoplasmic ratio (Fig. 1).

Case 2. Mrs. T. J., aged 60, para 1-1-0-0-1, entered the hospital with a complaint of vaginal bleeding of 3 to 4 weeks' duration. Her menses had begun at the age of 12, occurred every 28 days, and lasted 7 days. The last regular period had appeared at the age of 48, about 12 years previously. There had been no further bleeding until the present illness. She had hypertension of many years' duration; despite this she had no other complaints. The physical examination revealed a well-developed and well-nourished Negro woman. The blood pressure was 180 systolic and 100 diastolic. The somatic findings otherwise were unremarkable. After the electrocardiogram, x-ray of the chest, and

renal function tests were found to be within normal limits, the medical consultant gave clearance for operation. The pelvic examination was interesting. The uterus was found to be of a size compatible with a 3 months' pregnancy, probably due to the presence of fibromyomas. There were no palpable masses in either adnexal region. Because of the postmenopausal bleeding a diagnostic curettage was done. The tissue that was removed failed to reveal abnormalities in the endometrium. In view of the bleeding, the size of the uterus, and the possibility of malignancy still being present, a total hysterectomy and bilateral salpingo-oophorectomy were performed. The postoperative course was uneventful. After the patient was discharged she and her family moved to Florida. It was learned that shortly after her arrival there she again became seriously ill and died. Our communication led us to believe that death resulted from extension and metastasis of the original lesion. An autopsy was not obtained.

Pathology report.

GROSS. The specimen consisted of a totally resected uterus with both tubes and ovaries (Fig. 2). It measured 13.0 by 8.0 by 6.0 cm. and was submitted partially opened. The fundus was badly distorted by large round tumors, one measuring 6.5 cm. in its greatest diameter and located in the posterior wall and one measuring 4.5 cm. in its greatest diameter and located in the right cornu. Numerous smaller nodules, varying in size, were located in the wall of the uterus. The endometrial cavity measured 6.0 by 9.0 cm. The posterior wall was replaced by a tumor which broke through into the endometrial cavity in an area measuring 5.0 cm. in diameter. The tumor was of fairly firm consistency and ulcerated the endometrial surface. On section, the cut surfaces presented a mottled picture of yellowish gray necrotic areas interrupted by hemorrhagic as well as gray cartilage-like areas and grayish white areas of ossification. The tumor was fairly well circumscribed, but appeared to infiltrate the wall of the uterus. The remaining nodules were well circumscribed, firm in consistency, and showed on section a grayish white, fascicular structure. A narrow grayish red polypoid structure, measuring 2.0 by 1.0 cm., arising from the posterior wall was found. The endocervical canal measured 5.0 cm. The mucosa was slightly trabeculated and hemorrhagic. The vaginal os of the cervix was transverse and measured 1.0 cm. in diameter. The lips of the cervix were smooth, grayish red, and slightly hemorrhagic. The external surface was apparently covered by old fibrous adhesions, which were released by sharp dissection. The left tube measured 11.0 by 0.4 cm. The fimbriated end was apparently obliterated and adherent to the ovary which was very small, measuring 2.0 by 2.0 by 1.0 cm., and of firm consistency. On section, it was found to contain a calcified nodule measuring 1.0 cm. in diameter. There were numerous small cysts in the tuboovarian ligament which varied in size and which were filled by a clear straw-colored fluid. The right tube measured 13.0 cm. in length. The proximal end measured 0.5 cm. in diameter. The distal end showed a saccular dilatation measuring 2.5 cm. in diameter and containing a brown fluid. The ovary on this side measured 3.0 by 1.5 by 0.5 cm. It was firm, grayish yellow in color, and showed on section a slightly hemorrhagic, but generally smooth, grayish yellow appearance.

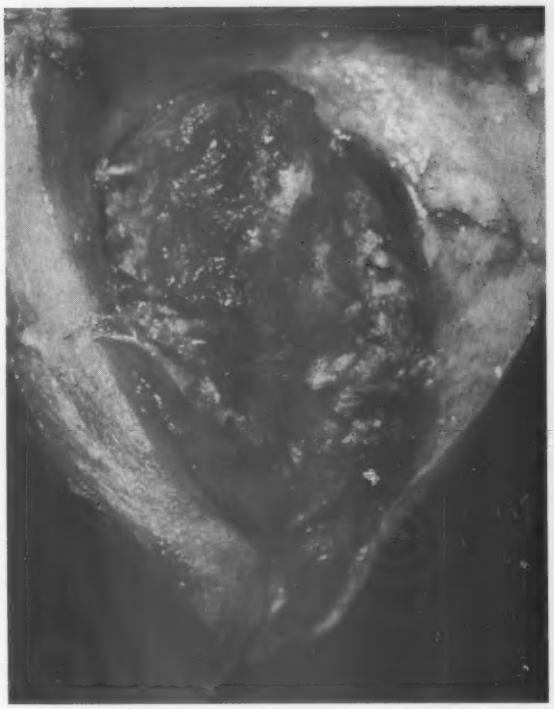

Fig. 2. Case 2. Gross specimen.

MICROSCOPIC. Sections through the tumor show areas in which osteoid tissue is being formed and in which calcium is present. The surrounding tumor tissue is composed of a dense cellular proliferation in which frequent mitoses were encountered (Figs. 3 and 4).

Case 3. This 71-year-old white woman, Mrs. A. R., a para 13-13-0-0-13, entered the hospital with a history of vaginal bleeding of 2 weeks' duration. Menses had begun at the age of 12, appeared every 28 days, and lasted 5 days. The last regular period had occurred 21 years prior to the onset of this illness; she had had no further bleeding up to the present time. The other phases of her history were unessential.

At the time of the physical examination the patient was found to be markedly obese but otherwise well developed. The blood pressure was 180 systolic and 120 diastolic. The general physical examination was unremarkable. Upon pelvic examination a necrotic foul-smelling mass was found protruding through the cervix into the vagina. The uterus and adnexa were difficult to palpate because of the obesity. Because of the patient's age she was completely evaluated from the standpoint of cardiac and kidney function. They were found to be essentially within normal limits. The vaginal mass was removed and a curettage performed. The microscopic examination of this tissue revealed elements of a mixed mesodermal tumor of the uterus. A secondary operative procedure was done; the uterus, both tubes, and ovaries were removed. The postoperative course was uncomplicated except for a superficial wound breakdown. It has been one year since operation and the patient is entirely well except for the presence of bilateral inguinal nodes. She refuses to allow a biopsy of them; she seems to be completely well.

Pathology report.

GROSS. The specimen consisted of a totally removed uterus and adnexa (Fig. 5). The uterus measured 8.0 by 12.0 by 4.0 cm. Situated subserosally was a tumor mass measuring 1.5 cm. in its greatest axis. On section, it presented bulging cut surfaces, with a typical whorled-like architecture. The endocervical canal measured 5.0 cm. in length. The mucosa was trabeculated and presented several cysts containing glairy material. The endometrial cavity measured 6.0 by 6.5 cm. The endometrium was markedly thickened and piled-up, measuring up to 0.3 cm. in thickness. It also presented several polypoid projections, the largest of which was situated at the left cornu and measured 2.5 by 1.0 by 0.5 cm. These polypoid masses were soft and some of them presented hemorrhagic cysts. The myometrium measured 1.5 cm. in thickness at the fundus. It was firm. Submitted separately were both tubes and ovaries. The tubes measured 9.0 and 10.0 cm. in length. The fimbriated ends were patent. The ovaries measured

Fig. 3. Case 2. High-power photomicrograph.

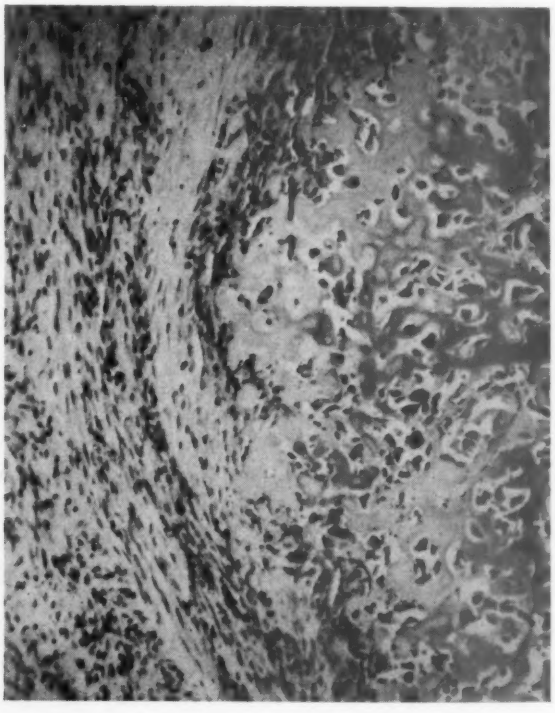

Fig. 4. Case 2. Low-power photomicrograph.

2.0 by 1.5 by 1.0 cm. and 2.0 by 1.0 by 0.3 cm. They were atrophic and on section the cut surfaces were not remarkable. Situated within the tuboovarian ligaments of one of the adnexa was a round, lobular, firm yellow body measuring 0.3 cm. in diameter.

MICROSCOPIC. Sections of the tumor showed nests of cartilage-like cells surrounded by sheets of closely arranged, medium-sized spindle- and oval-shaped cells possessing round and oval nuclei with scanty cytoplasm. They exhibited some variation in nuclear size and chromaticity. Scattered mitoses were present. Nests of cartilage were found in juxtaposition to glandular formations lined by columnar cells (Figs. 6 and 7).

Comment

It is apparent from a thorough study of the pathology findings of the specimens in 2 of our reported cases that the diagnosis of mixed mesodermal tumor should be considered. One was distinctly labeled as this type. The osteogenic sarcoma, when completely studied, suggested the possibility of a mixed mesodermal tumor. The third case of fibromyxosarcoma was found to be an extremely malignant type of tumor with rapid deterioration and death. Mixed mesodermal tumors also are extremely malignant and usually are rapidly fatal. This is confirmed by the course of our patients and the review of Glass and Goldsmith,[7] who reported a death rate of 90 per cent within the first year following operation.

We agree with most authorities that the presence of myoblasts in these tumors is not a prerequisite for a diagnosis of mixed mesodermal tumor. The presence of a single element of heterologous or homologous tissue, as well as the other malignant connective tissue features, is sufficient to justify the classification of this type of new growth.[17]

We cannot add new data to the histogenic theories of the development of mixed mesodermal tumors. We are inclined to favor Willis' attitude since it is difficult to believe that "rests" of tissue remain dormant in the uterus throughout a whole menstrual life and then suddenly become rejuvenated.

The treatment of connective tissue tumors by radiation has always been of questionable value.[2, 3] However, it is impossible to

Fig. 5. Case 3. Gross specimen.

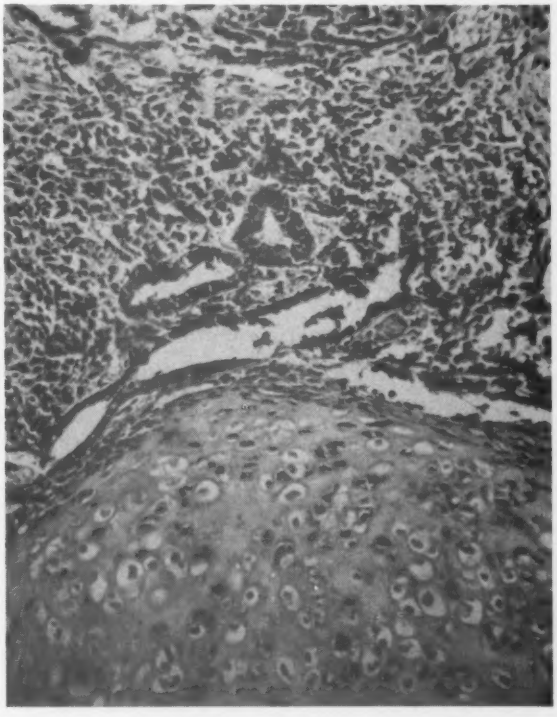

Fig. 6. Case 3. High-power photomicrograph.

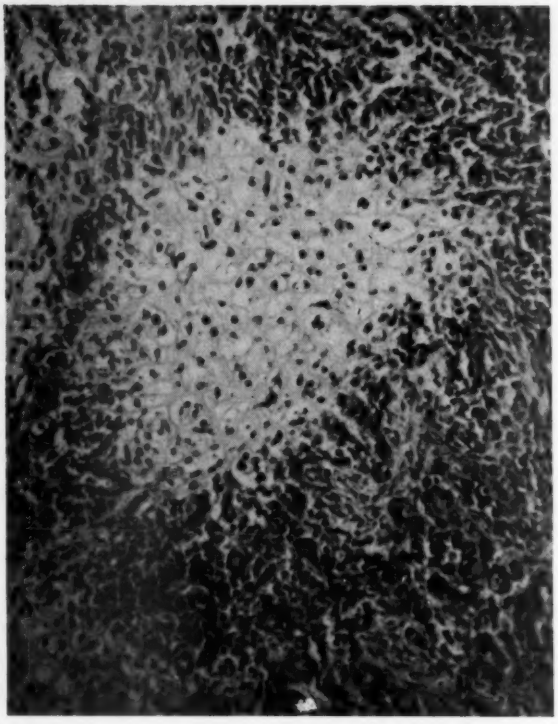

Fig. 7. Case 3. Low-power photomicrograph.

generalize. Most authorities believe that each case should be individualized. If evidence of extension or metastasis appears early this therapy should be instituted in an attempt to allay rapid spread, pain, and other distressing symptoms.[3] It has been our experience that this kind of treatment has not alleviated the pain, delayed the formation of metastatic lesions, or enhanced the patient's recovery. We believe that the use of radiotherapy raises false hopes and impressions. Paradoxically it would seem that x-ray therapy should be beneficial because of the embryonal nature of mesenchymal tumors. The high mortality rate indicates that neither operation nor x-ray therapy is effective in delaying an early death.

It is our impression that mixed mesodermal tumors occur more often than quoted in the literature. Perhaps a more thorough search of the microscopic sections cut from the specimen of bizarre sarcomas would result in a report of higher incidence. The diagnosis is very rarely made by curettage specimens as is also true in sarcoma of the uterus. An early diagnosis with complete surgical extirpation probably offers the best choice of recovery.

Summary and conclusions

1. The pathology, histogenesis, location, and clinical course of mixed mesodermal tumors has been reviewed.

2. The case histories of 2 patients with mixed mesodermal tumors and one patient with a bizarre type of sarcoma of the uterus have been presented.

3. Mixed mesodermal tumors are comparatively rare, although we suspect that a more thorough search of the microscopic sections would raise the incidence considerably.

4. We feel that it is not necessary to find evidence of myoblasts in order to adjudge a specific tumor to be classified as this variety.

5. Mixed mesodermal tumors are extremely malignant and metastasize early. The treatment of choice is complete surgical extirpation. X-ray therapy is of questionable value even in specific cases.

We wish to express our gratitude to Dr. William Lovitt, pathologist for The Hospital for the Women of Maryland, and to Drs. Tobias Weinberg and Robert Solomon, pathologists for the Sinai Hospital, for their reports on the pathology findings in these cases. We also wish to express our thanks to Dr. A. A. Sondheimer, chief of the Gynecological Service of Sinai Hospital, for his helpful criticism and stimulation in the preparation of this manuscript.

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OBSTETRICS

Plasma aminopeptidase activity (oxytocinase) in pregnancy and labor

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THE ability of pregnancy plasma to inactivate oxytocin was first observed by Fekete[1] in 1930 and has since been studied by a number of investigators. In 1946, Page[2] described an enzymatic unit for "pitocinase" (now an inappropriate term) based upon the time required for 50 per cent destruction of the substrate. The rate of oxytocin inactivation was determined by serial bioassays on the isolated rat uterus.

Despite the inaccuracies of the bioassay, Page[3] noted in 1947 that pregnancy could be diagnosed as early as 4 weeks after conception; and that during the first half of normal pregnancy, the time of conception could be estimated with an accuracy of ±5 days. The values obtained at term were no doubt higher than the true inactivation rates in vivo, because the plasma samples were diluted. Gonzalez-Panizza and associates[4] demonstrated that a progressive dilution of pregnancy plasma produced less than the expected decrease of enzymatic activity. This is probably due to the presence of an inhibitor to oxytocinase in plasma, and dilution reduces the inhibitor activity more than it reduces the enzyme activity. Thus, the true increment of oxytocinase activity due to pregnancy is probably between 50 and 100 times, as described by Werle and Semm,[5] rather than a thousandfold as described earlier.[2, 3]

Most observers have failed to find any changes in plasma oxytocinase prior to or during labor. In 1959, however, Hilton and Johnson,[6] utilizing the same type of rat uterus bioassay, reported that the oxytocinase activity of plasma decreased to zero or near zero in 6 of 9 women studied during the first stage of labor. A similar decline had been reported by Namiki[7] in 1952, and by Dicker and Tyler[8] in 1954, although denied by Dicker and Whyley[9] in 1959. If true, this would be of considerable theoretical importance be-

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This investigation was supported by Training Grant 2G-145 from the National Institutes of Health and by a grant from the Association for the Aid of Crippled Children.

cause it might explain the cause of labor in primates. Oxytocinase, incidentally, exists only in the plasma of pregnant women and monkeys, and not in other species.

Cystine aminopeptidase

The structure of the oxytocin molecule was announced independently by Tuppy[10] and by Du Vigneaud and co-workers[11] in 1953. It is an octapeptide amide, and the relationship of cystine in the cyclic pentapeptide moiety is shown in Fig. 1. In 1957, Tuppy and Nesvadba[12] demonstrated that when synthetic oxytocin is acted upon by human pregnancy plasma, the ring is split between cystine and tyrosine and the hormone thus became inactive. They proved this by adding performic acid to the inactivated product to split the disulfide linkage, thus liberating the cysteine fragment. These experiments led them to conclude that the primary oxytocin-inactivating enzyme of pregnancy plasma was a cystine aminopeptidase.

In 1958 Müller-Hartburg, Tuppy, and Nesvadba[13] described a synthetic substrate for determining cystine aminopeptidase activity. This compound, cystine di-β-naphthylamide, is illustrated in Fig. 2. When acted upon by pregnancy plasma, two molecules of β-naphthylamide are released which can be converted to a compound readily measured by colorimetry. The synthetic substrate is apparently split more readily than oxytocin by other nonspecific aminopeptidases found in nonpregnancy plasma, since nonpregnancy values are relatively high when compared to the biologic assay method which uses oxytocin as the substrate. The chemical method is unsatisfactory, therefore, for the diagnosis of early pregnancy. The colorimetric method, nevertheless, is vastly simpler and considerably more accurate, thus compensating for some loss of specificity.

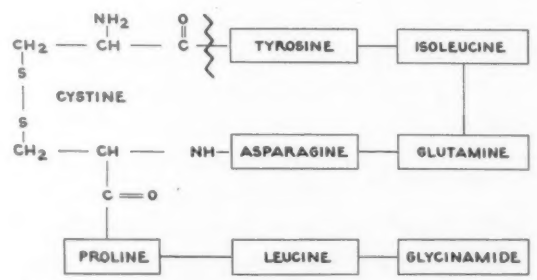

Fig. 1. Structure of oxytocin, designed to show the point at which the cystine-tyrosine linkage is split by pregnancy plasma.

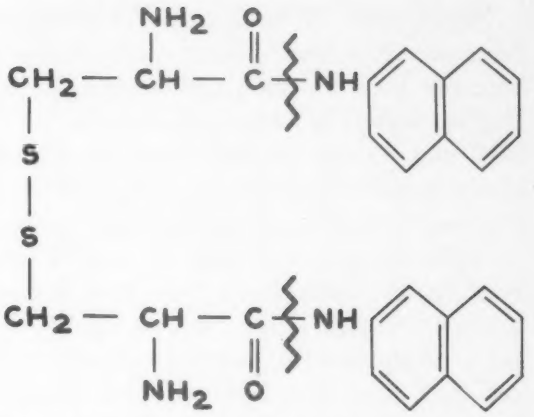

Fig. 2. Structure of the synthetic substrate, cystine di-β-naphthylamide, showing the linkages split by cystine aminopeptidase.

Method

The chemical method of oxytocinase assay is based mainly upon the Bratton-Marshall reaction, as modified by Tuppy and Nesvadba.[12] It is described here with minor modifications and additions for those who might wish to carry out the procedure.

Blood sample. Hemolysis of the drawn blood is avoided by emptying the syringe slowly and refraining from forcibly expelling any residual foam. Serum is usually used. Heparinized plasma and serum from the same sample of blood give identical values for aminopeptidase activity. The serum can be kept in the refrigerator for 48 hours or in the freezer for months with no change in the activity.

Reagents.

Substrate solution. L-cystine-di-β-naphthylamide,* 135 mg., is dissolved in 50 ml. of 0.012 N HCl, with moderate warming. The clear solution is diluted to 100 ml. with distilled water and stored in the refrigerator.

*May be obtained from Sanabo Company, Anton-Scharff-Gasse 7, Vienna.

Buffer. (pH 7.9) 68.9 ml. of 0.1 N sodium Veronal (20.6 Gm. sodium diethyl-barbiturate per liter of boiled carbon dioxide–free distilled water) is mixed with 31.1 ml. 0.1 N HCl and 50 ml. distilled water. If the pH of the buffer is not 7.9, it is adjusted (glass electrode), then stored in the refrigerator.

Other reagents. Trichloracetic acid, 10 per cent (w/v); hydrochloric acid, 0.36 normal acetone, reagent grade; sodium nitrite, 0.1 per cent aqueous; ammonium sulfamate, 0.5 per cent aqueous; ethylenediamine-dihydrochloride (Eastman Kodak), 0.1 per cent, aqueous.

Standard β-naphthylamine. Eighty milligrams of β-naphthylamine is dissolved in 500 ml. 0.012 N HCl with warming and stirring, and diluted to one liter with distilled water. The solution is stored in the dark.

Method. Serum, 0.6 ml., is diluted with 0.9 ml. water and 3.0 ml. Veronal buffer; 0.75 ml. of the diluted serum is pipetted into each of 3 centrifuge tubes. The first of the 3 tubes serves as the zero time control. Into it is pipetted 0.25 ml. of substrate solution followed immediately by the addition of 1.0 ml. of 10 per cent trichloracetic acid. The remaining tubes (duplicates) are placed in a water bath at 37° C. and 0.25 ml. substrate solution is added to each. After 4 hours at 37° C., the reaction is stopped by the addition of 1 ml. of 10 per cent trichloracetic acid. After shaking, the tubes are centrifuged, and 1.0 ml. of the clear supernatant solution is pipetted into a 50 ml. Erlenmeyer flask. (If time does not permit the development of color on the same day as the enzyme reaction, these flasks may be stoppered and stored in the refrigerator overnight.)

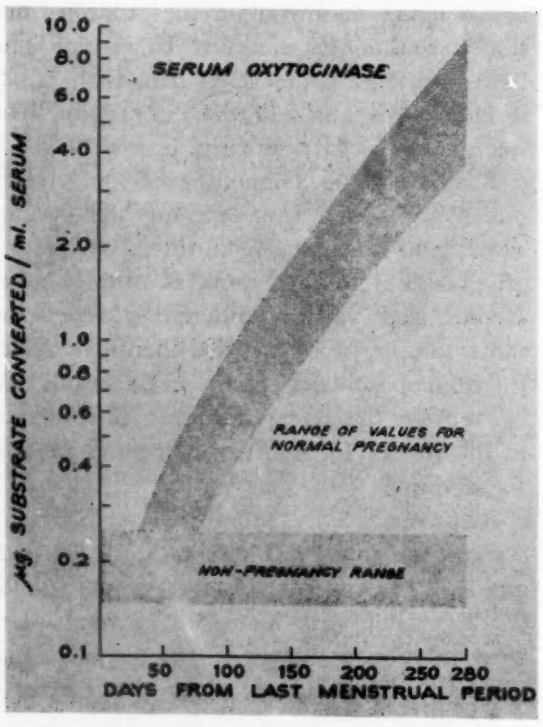

Fig. 3. Shaded area includes 95 per cent of the 110 plasma cystine aminopeptidase determinations during normal pregnancy.

A reagent blank and standards are set up as follows: 1.5 ml. of water is mixed with 3.0 ml. buffer, and 0.75 ml. of the resulting solution is pipetted into each of 3 tubes. To the reagent blank is added 0.25 ml. of water and, to the standards, 0.25 ml. of the standard β-naphthylamine solution. These tubes are then treated in the same manner as those containing serum.

Color development. To each flask containing 1 ml. of filtrate is added 9 ml. of a mixture of 2 volumes of 0.36 N HCl and one volume of acetone. The flasks are carried to a dark room lighted only with a small red lamp. The following additions are made 3 minutes apart and the flasks are mixed by rotation after each addition: 1 ml. sodium nitrite, then 1 ml. ammonium sulfamate, and last, 1 ml. ethylenediamine dihydrochloride. The flasks are stoppered and set in an incubator in the dark at 37° C. for 4 hours. The maximal color is reached after 3 to 4 hours and remains constant for several hours. After cooling to room temperature, the samples are read in a spectrophotometer at 565 mμ.

Calculation. $\frac{\text{O.D. unknown} - \text{O.D. control}}{\text{O.D. standard} - \text{O.D. blank}} \times 5 =$ milligrams of β-naphthylamine liberated per 100 ml. serum per hour.

The measure of aminopeptidase activity is expressed as the number of milligrams of β-naphthylamine liberated per 100 ml. of

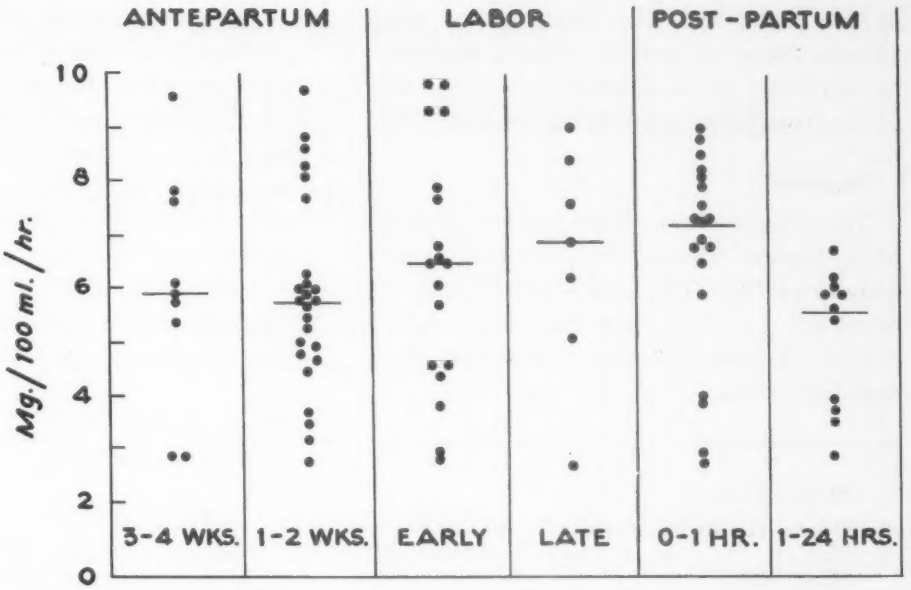

Fig. 4. Scatter of aminopeptidase values during the last month, early and late labor, and the immediate puerperium.

undiluted serum per hour from the substrate. The value of the factor

$$\frac{5}{\text{O.D. standard} - \text{O.D. blank}} = 20.5 \text{ (average)}$$

when the Coleman Jr. spectrophotometer is used with 12 by 75 mm. round cuvettes.

The standard solution described represents a value of 5.0 mg. β-naphthylamine per 100 ml. serum per hour, which is equivalent to the average value of cystine aminopeptidase activity found in the serum of pregnant women at term.

Results

When this reaction was applied to nonpregnancy and to pregnancy plasma samples, 95 per cent of 110 determinations fell within the shaded areas shown in Fig. 3. The activity of nonpregnancy plasma is due to a mixture of aminopeptidases, some or all of which show moderate increases in pregnancy. According to Tuppy,[14] however, human pregnancy is characterized by the appearance of a new aminopeptidase which cannot be detected in the blood of nonpregnant individuals. The presumption is that this enzyme arises from the placenta or decidua, but this has not been proved.

Individual values obtained during the month prior to labor, during early or late labor, and during the early puerperium are shown in Fig. 4. No significant trends are in evidence. The wide scatter is due to differences between individuals and not to the presence or absence of labor. This is demonstrated in Fig. 5, in which serial values on the same individuals are shown before, during, and after labor. From these data, we may conclude that there are no declines in the oxytocinase activity of plasma at the end

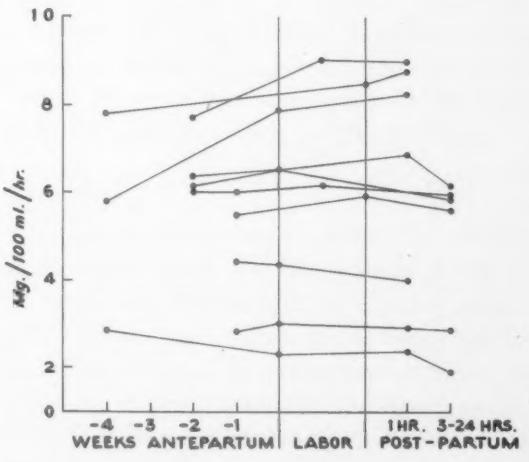

Fig. 5. Selected data from Fig. 4, plotted for individual patients.

of pregnancy and that the onset of spontaneous labor in women cannot, therefore, be attributed to a diminution in the ability of the blood to destroy endogenous oxytocin.

Summary

The primary oxytocinase activity of pregnancy plasma is apparently due to a cystine aminopeptidase. The latter activity may be measured by a chemical procedure which utilizes the synthetic substrate cystine-di-β-naphthylamide.

The results of 110 determinations during pregnancy indicate a progressive rise of this aminopeptidase activity in plasma, paralleling the oxytocinase curves obtained by biologic assay methods. Contrary to some reports, there is no decline of activity during early or late labor, parturition, or the early puerperium. The onset of spontaneous labor in women can hardly be attributed to a diminished ability of the plasma to inactivate endogenous oxytocin.

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Effect of anoxia during labor and immediately after birth on the subsequent development of the child

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THE purpose of this study is to determine the effect of anoxia during labor and after birth on the subsequent development of the child.

The obstetrician is seldom aware of neuropsychiatric disorders which develop in children subsequent to birth. These are rarely apparent during the neonatal period and if they are later brought to his attention it is usually accidentally by the mother who seeks advice regarding consultation with a neurologist or psychiatrist. In order to become aware of these ailments it is imperative to follow the growth of the child for at least a period of one year after birth since symptoms are not ordinarily apparent until the child is at least 6 months of age.

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This study was made possible by a grant by the Research Society for Cerebral Palsy.

Presented at a meeting of the Chicago Gynecological Society, April 17, 1959.

Benda[1] urges concern for quality as well as survival of the offspring. He finds that 6 children out of every 100 are exceptional in that because of emotional difficulties, psychotic derangements, or intellectual inadequacies they are not fully equipped to meet the requirements of a standardized community life. He also notes that one child in 1,500 is spastic. Many such exceptional children survive and require medical or custodial care over a period of 50 to 60 years. Each of these conditions has been associated with anoxia at birth. If such an association is factual the obstetrician needs to become aware of the magnitude of the problem.

Anoxia

Anoxia is said to occur when the oxygen supply falls below the physiologic needs of the organism. This definition is not as rigorous as the statement appears to imply and is actually too vague for practical purposes in research. It rests upon the ability to determine the physiologic limits of tolerance of the organism. Even a decrease in the oxygen saturation of the blood as determined

by chemical analysis does not necessarily mean that the fetus suffers serious alterations in physiology.[2, 3] The exact level at which function is altered is unknown in the human being. The situation may be somewhat different in animal experimentation since no restraint need be placed upon the production and measurement of pathologic effects.

Smith[4a, 4b] states that the oxygen economy of human life before birth remains uncertain and that the change in the low levels of saturation of the fetus to the 95 per cent saturation of the infant at 3 hours after birth is the most essential adjustment made by the newborn infant. The rate and degree of this adjustment are not constantly related to the degree of anoxia shown in cord blood at birth or with complete expansion of the lungs.

Pennoyer and associates[5] have shown that cord blood oxygenation at birth and arterial blood oxygenation up to one hour are decreased in infants who require oxygen resuscitation. Even with the administration of oxygen these infants show inferior oxygenation throughout the first hour of life, and 43 per cent are still below the normal 90 per cent saturation level at the end of one hour. They believe that maternal complications during pregnancy and labor and signs of fetal distress may be valid indicators of intrauterine anoxia.

In the present communication anoxia is defined in terms of the clinical condition. It is assumed that the apneic child who experiences a lack of pulmonary ventilation due either to intrauterine asphyxia, obstruction of the airways, sedation, or a combination of these factors and who displays subsequent respiratory difficulties such as partial atelectasis, hyaline membrane disease, or pneumonia suffers a degree of oxygen deprivation.

Neuropathologic sequelae

Ever since Freud[6] in 1897 first challenged Little's[7a, 7b] belief that asphyxia neonatorum is concerned with the later development of cerebral palsy and other conditions, the theory which associates anoxia at birth with the later development of neuropsychiatric disorders has advanced or receded in popularity. Today the concept rides the crest of the wave and has been restated by Lilienfeld and associates[8a-8f] as the "continuum of reproductive casualty." The "continuum of reproductive casualty" assumes that as a result of abnormalities of pregnancy and labor, brain damage may be incurred leading to a gradient of injury with a lethal component resulting in fetal or neonatal death and a sublethal component leading to the development of neuropsychiatric disorders. In a series of retrospective studies from 1951 to 1955 these men found a direct association between the complications of pregnancy and labor usually accompanied by anoxia and the subsequent development of cerebral palsy, epilepsy, mental retardation, and behavior problems. The observations of Schreiber,[9a-9d] Darke,[10] Preston,[11] Gesell and associates,[12] Despert,[13] Stevenson,[14] and Eastman[15] based on statistical clinical research support this hypothesis.

On the other hand, the work of Hannes,[16] McPhail and co-workers,[17] Penrose,[18] Struma,[19] Keith and associates,[20] Apgar and co-workers,[2] Usdin,[21] Campbell and associates,[22] and Benaron and others[23] fails to support the hypothesis that sublethal injury from anoxia manifests itself as organic damage to the brain. They find no correlation between anoxia at birth and the subsequent development of neurological lesions, mental retardation, and/or behavior problems.

Nor is there uniform opinion among pathologists regarding the effect of anoxia at birth on the cerebral architecture. Schreiber[9] and Benda[1] believed that specific lesions do occur which persist throughout life and can be demonstrated at the time of death. On the other hand, Zuelzer[24] stated that such lesions are not specific to anoxia and that any association is not based on fact but on inference only. Ford[25a, 25b] tends to agree.

Courville[26] has demonstrated that structural changes take place in the adult brain after exposure to severe anoxia. He con-

cludes that similar changes occur in the brain of the newborn infant. This argument disregards the evidence that the brain of the newborn infant is much more resistant to oxygen deprivation than the adult brain. Some fetal pathologists feel that many cerebral hemorrhages attributed to anoxia at autopsy are purely a manifestation of a terminal state.[27-29]

The fetus or newborn infant has a physiology peculiar to its time of life which protects it from variations of oxygen supply incident to labor and delivery which might otherwise prove fatal.[30a, 30b, 30c, 31, 32] Himwich,[33a, 33b] has shown that the newborn of various species survive oxygen lack longer than the adult and that the lower brain of the dog and rat utilizes more oxygen than the cerebrum until one month of age when the reverse is true. On the other hand, Benaron and co-workers[34] have shown that the human brain is biochemically more advanced than that of either the dog or rat. The cerebrum utilizes more oxygen than the lower brain from 30 weeks of gestation to term. Various species vary in their ability to withstand oxygen lack. This appears to depend on the degree of maturation of the fetus[33, 35a, 35b] at birth. Because of these variations one cannot unreservedly apply conclusions drawn on animal experimentation to the human being.

Intellectual and behavioral development

Apgar and associates[2] found no relationship between anoxia at birth defined in terms of arterial blood oxygen saturation and subsequent development.

Graham and others[36a-36c] found a direct correlation between clinical anoxia at birth and performance on behavior tests devised to determine motor and sensory responses during the first few days of life and are hopeful that these tests will detect brain damage which will be reflected in the later development of the child. This possibility may be entertained but would necessitate direct experimental evidence to be acceptable. There is a preponderance of evidence to show that behavior tests during the first year or so of life have little value in predicting the individual's intelligence in later life. However, in a follow-up study of these children, Ernhart and associates[37] reported small but statistically significant differences at the age of 3 years between the apneic children and the control group on an intelligence test and a vocabulary test. There are no obvious defects which differentiate these children from the controls. Rather, the group as a whole shows somewhat less adequate performance.

Population studied

The Chicago Maternity Center serves the underprivileged people in the city and these are predominantly Negro. The population is as homogeneous a socioeconomic group as is possible to obtain in respect to poverty and lack of opportunity for social and economic advancement. All of the deliveries, both spontaneous and instrumental, are conducted in the home. Operative delivery, with the exception of version, is performed under regional or saddle block anesthesia. The incidence of syphilis, illegitimacy, metabolic disorders, and unattended birth among the mothers is high.

During the 15 year period, Jan. 1, 1938, to Jan. 1, 1953, inclusive, there were 40,960 babies born on the home service of the Chicago Maternity Center. Documented birth records are available for all patients cared for by the Center. Of the total population at the Center 2,458 babies, or 6 per cent, were apneic at birth. Of the apneic children, 251 were in unsatisfactory condition after resuscitation and required either hospitalization or prolonged observation in the home. Forty-three of the most seriously affected were selected for the study. These represent what we consider the most profoundly anoxic children in a group of over 40,000 newborn infants. In all, 97 children, 43 anoxic and 54 controls, drawn from this population were studied.

In making a choice of children for study, not only were the degree and duration of apnea considered but the complications of

labor and delivery which led to the lack of pulmonary ventilation and the subsequent development of respiratory complications following resuscitation were also evaluated. For instance, a child who was apneic at birth whose mother during labor lost 500 c.c. of blood from abruptio placentae and who, after resuscitation, subsequently developed pneumonia would be chosen instead of a child who, after a difficult operative delivery, had severe apnea but appeared in excellent condition one hour after birth.

Contact was made with 41 of the 43 children chosen for study. None of these had any apparent neuropsychiatric disorder at the time of the examination. Thirty cooperated and were examined and tested. Eight refused examination but gave a developmental history and the family was visited. Five could not be reached. Some knowledge was available on 3 of the children who could not be reached. One child died in a fire at 3 years of age. The mother said that this child had been healthy and bright. Case workers reported that 2 of the children whose families had left town appeared normal in regard to growth and development when last seen. There was no knowledge of the remaining 2 children.

Two control groups were available from the same population as the apneic children. One of these groups consisted of siblings of the affected group. These were of the same sex and as near the age of the anoxic child as was available in the family. The mothers of these controls had experienced natural labor, and birth was without anoxia. There were 14 such controls available. The second group was made up of 10 white males, 10 Negro males, 10 white females, and 10 Negro females whose mothers had experienced natural labor and spontaneous deliveries and whose respiration was immediate and spontaneous. Some of the results on this latter control group have been reported before by Benaron and associates.[23] Of the anoxic children 20 were males and 10 females. There were 22 Negro and 8 white children. Of these 11 were first-born children. The 14 anoxic children and the sibling controls were distributed as follows for each group: 8 males and 6 females; 12 Negro and 2 white.

At the time of the examination the children ranged in age from 3 to 19 years. The average age for the anoxic group was 10.2 years; for the 14 anoxic children where sibling controls were available the average age was also 10.2 years; for the sibling controls, 11.2 years; for the 40 additional controls, 10.4 years.

The anoxic children

Among the 30 children who suffered anoxia, apnea was severe in 24 and moderate in 6. A baby is apneic who does not breathe within 30 seconds of birth. Flagg's[38] 1931 classification of apnea has been used. In severe apnea, the baby appears dead; it is either livid or pallid. All superficial and deep reflexes are absent and there are signs of circulatory failure. The heart rate is slow, irregular, and at times barely discernible. The incidence of death among severely apneic children is high. In moderate apnea the superficial reflexes are absent and the baby gasps occasionally.

The duration of apnea ranged from 10 to 30 minutes for 19 of the children, from one half to one hour for 7, and over one hour for 4; although as far as prognosis for survival is concerned the degree of apnea is more important than the duration.

The chief cause of apnea in 23 children was intrauterine asphyxia. The causes for this condition are summarized in Table I. In half of these cases intrauterine distress was indicated by persistent slowing in fetal

Table I. Causes of intrauterine asphyxia

Condition	*No.*
Breech with arrested head	6
Gigantism with arrested shoulders	2
Prolonged labor with spontaneous delivery	1
Prolonged labor with operative delivery	6
Placental dysfunction	1
Rapid hard labor	4
Abruptio placentae	2
Cord compression	1

heart rate and/or well-mixed meconium in the amniotic fluid.

Twice apnea was due to obstructed airways caused by complications of unattended birth, caul once, and massive aspiration of amniotic fluid once. Sedation alone accounted for 5 cases and contributed to 11 others. No general anesthesia was used in any of the labors.

For the purposes of analysis of the data which were collected, the 30 children who cooperated in all of the examinations could be divided into three groups on the bases of the severity of the anoxia. These were as follows: Group I consisted of 11 children with the most severe apnea with prolonged respiratory difficulties due to asphyxia and sedation who were hospitalized at birth. Group II consisted of 9 children who were considered to be less affected than those in Group I. The mothers received no sedation, but the children were severely apneic at birth and they were all hospitalized because of respiratory difficulties. In 7 cases the apnea was due to intrauterine asphyxia and, in 2, to complications of unattended birth. Group III consisted of 10 children considered to have the least severe apneic condition. In 5 of these cases the mothers were sedated. Six of the children had severe and 4 moderate apnea at birth. Respiratory difficulties were prolonged but not of the severity to necessitate hospitalization.

All of the children had prolonged respiratory difficulties following the initial resuscitation, which required repeated aspiration and artificial respiration. These difficulties were characterized by excess mucus, Cheyne-Stokes respiration, cyanotic spells, lack of body tone, and intercostal retraction. Twenty were hospitalized from 2 to 150 days. The average hospital stay was 14 days. All were discharged in satisfactory condition.

Incidental conditions were fractured clavicle, cephalhematoma, and congenital hypospadius. In 3 cases there was spasticity of the neck, and in 3 others spasticity of one or more extremities. A diagnosis of tetraplegia was made on one child and this child dragged the right leg for 8 years. Three of the children had premature births. The birth weights were less than 2,500 grams for 3, from 2,500 to 5,500 grams for 25, and over 5,500 grams for 2.

Procedures

After a selection of the anoxic children and the controls was made from the medical records of the Chicago Maternity Center, the parents of these children were interviewed and their cooperation obtained. A case worker from the Department of Psychiatry obtained a history of the child. The children were then brought to the Northwestern University Medical School for the examinations to be conducted.

The child was given a physical, neurological, and psychological examination by a pediatrician, neurologist, and psychologist. The personnel who conducted these examinations were unaware of the condition of the child at birth.

The psychological tests were designed to evaluate the mental development of the child, the possibility of the presence of organic brain damage of the higher neural centers, and the emotional adjustment and personality. For these purposes the following tests were administered: Stanford-Binet, Form L, Draw-a-Person, Bender-Gestalt, figure completion, Yacorzynski[39] Battery for Cortical Involvement consisting of the illusions and ambiguous figures, laterality tests, and the Rorschach test. In this report the main emphasis is placed upon the intellectual factors which were evaluated and upon the potentiality of organicity, a term meaning organic involvement of the higher neural centers of the brain.

In the physical examination conducted by a pediatrician, specific data, exclusive of the birth experience, was obtained from the mother and school placement was recorded. A complete physical examination was made on each child and the weight and height measured. A search was made for physical and developmental sequelae usually attributed to the child's birth experi-

Table II. Intelligence quotients and their dispersion among anoxic children and their controls

	No.	*Stanford-Binet I.Q.*	*Standard deviation*	*Goodenough I.Q.*	*Standard deviation*
Apnea	30	87.5	20.61	82.7	24.40
Controls	40	87.2	12.45	*	*
Apnea (with sibling controls)	14	83.0	15.57	77.9	21.76
Sibling controls	14	89.1	11.69	84.1	9.28

*Draw-a-Person test was not administered to this group.

ence—agenesis, spasticity, idiocy, hydrocephalus, mental retardation, asymmetry of any portion of the body, claw hands, or any minimal changes.

Besides the neurological examination, the majority of children had an electroencephalogram. Waking and sleep records were taken from bilaterally placed frontal, anterior temporal, temporal, parietal, and occipital electrodes. However, since the frontal leads were accidentally grounded on some of the patients, only the results obtained from the temporal, parietal, and occipital leads were considered in the data. Both monopolar and bipolar derivations were used. Whenever necessary, a record was obtained under sedation. Ambiguous records were checked by a second examination.

To determine whether anoxia at birth produced any later effect on the child the results were analyzed by appropriate statistical procedures by comparing the anoxic children and their sibling controls with the normal birth group selected at random from the same population.

Intellectual development

The intellectual development at the time of the examination could be evaluated by the child's performance on the intelligence tests, by his school placement, and by his developmental history. Besides by the Stanford-Binet test, the mental age of the child can also be measured by the Draw-a-Person test with the use of Goodenough's[40] scales, although the latter test is not as valid as the Stanford-Binet since an extremely low or a very high score cannot be evaluated.

Table II gives the average intelligence quotients of the anoxic children and the control children on these 2 tests.

We had previously analyzed the intelligence quotients between the males and females and Negro and white children and found that no difference was present among these groups. Consequently, each group can be compared with the other without the need to factor out these variables. Although Table II shows that the 14 controls are on the average about 6 I.Q. points higher than their siblings who were anoxic at birth, these differences are not statistically significant.

The variability or standard deviation is also given in the table for each of the groups. These results indicate that the anoxic group is more variable than the controls. That is to say, in the anoxic group there are more individuals with either high or low intelligence quotients than in the control group. These results are presented graphically in Fig. 1. It is seen that there were more children in the anoxic group with I.Q.'s over 110 than in the controls. In like manner, this group was characterized by a greater number of retarded children with I.Q.'s below 70. This latter result bears some significance when the total anoxic group is compared with the spontaneous normal delivery controls (chi squared = 6.25 with a probability between 0.05 and 0.02).

Among the 30 anoxic children 5 were definitely retarded in school in that they either failed 2 grades or were in an ungraded room in school. This was also true of 4 of the 54 controls in the spontaneous normal delivery group. These results indi-

cate that the anoxic children showed no statistically greater frequency of severe retardation in school than did children who were born under normal conditions.

The incidence of developmental disorders among the groups studied was determined from the case histories obtained from the parents by the psychiatry-trained social worker and by the examination of the subjects. These disorders include delayed maturation of normal functions and the persistence of infantile behavior. The classification which was used includes delayed appearance of walking, delayed appearance of talking, eneuresis past the age of 6 years, persistent infantile habits (such as thumb-sucking) past the age of 6, persistent infantile neuromuscular awkwardness, and retardation of mental development. The incidence of these developmental disorders are summarized in Fig. 2. The only factor which is statistically significant is the persistence of infantile habits in the anoxic children. In 63 per cent of the anoxic children there were infantile forms of behavior present, but this was so in only 26 per cent of the controls. As can be seen in Fig. 2, the incidence of developmental disorders per child in the anoxic group was approximately twice as high as in the controls.

Studies of organicity

Anoxia can be expected to have the greatest effect upon the higher neural centers of the brain. As a consequence, a major portion of the present research was oriented toward examining this potentiality. For this reason psychology tests especially designed for this purpose were used and the data examined for possible organic signs. In addition, neurology examinations were conducted on the children, an electroencephalogram was obtained, and the developmental history was examined for aspects which may indicate organicity.

Psychology tests. A number of comparisons were made between the children who underwent anoxia and the controls, as well as among the children in the anoxic group with different degrees of severity of the condition. These included the spread over the mental age years of the Stanford-Binet, the difference between the I.Q. of the Stanford-Binet and Draw-a-Person, the scores on the Bender-Gestalt, the illusions and ambiguous figures of the Yacorzynski test,

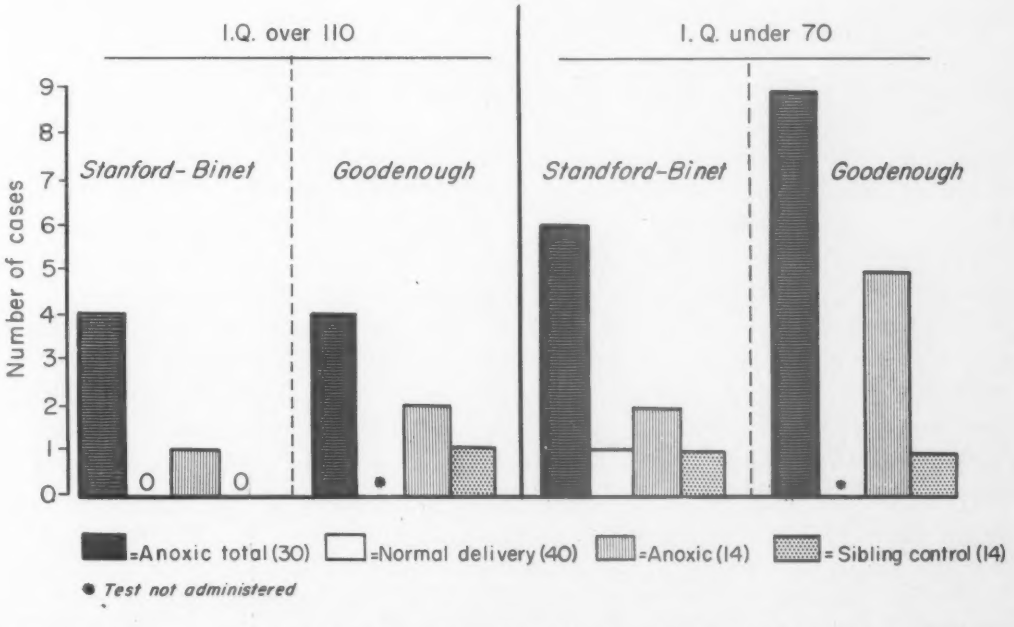

Fig. 1. Intelligence quotients of over 110 and under 70 of anoxic children and controls on the Stanford-Binet and Goodenough tests.

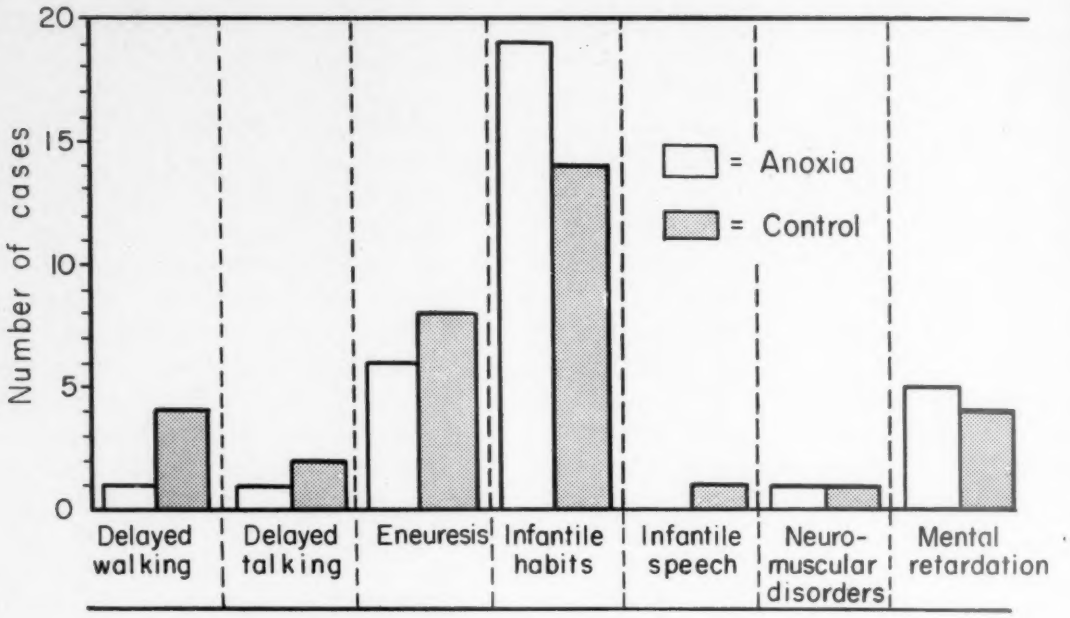

Fig. 2. Distribution of developmental disorders.

No. of children		*No. of disorders*		*Average disorder per child*	
Anoxic	30	Anoxic	33	Anoxic	1.1
Control	54	Control	34	Control	0.6

the results on the completion of the figures of the Stanford-Binet, and the tests for laterality. All of these factors in the psychological armamentarium have at times been considered to evaluate organicity of the higher functions of the brain. In general, the anoxic children obtained a lower score on most of these tests.

The greater variability of the anoxic group in relation to the controls already reported for the intelligence test (Table I, Fig. 1) was also characteristic of most of the other tests. Thus, the standard deviation for the anoxic children on the difference between the Stanford-Binet and the Draw-a-Person tests was 12.01, and for the controls 7.63; on the ambiguous figures the anoxic children showed a standard deviation of 10.06, and the controls of 4.36. This factor alone reduces any test of significance between the two groups.

The neurological examinations of the children in no instance yielded gross signs of dysfunction. The greatest degree of these minimal signs were present in 8 of the 30 anoxic children. However, approximately the same number of anoxic children fell into this category as their sibling controls (6 of the 14 anoxic children with sibling controls, and 4 of the siblings).

Fig. 3 summarizes the neuropsychiatric disorders evident in the subjects either from the case histories or from the examinations. These include epileptiform seizures, strabismus, behavior problems, emotional disturbance, focal neurological lesions, and stammering. The incidence of factors dealing more exclusively with the possibility of organic brain involvement (seizures and focal neurological lesions) were low or absent in each of the two groups of children with no significant difference between them. The highest incidence of these disorders deals with various symptoms of emotional disturbance. There were 27 in the anoxic group and 22 in the control group with these symptoms, which is not a significant difference.

The electroencephalographic studies were

conducted on 21 of the anoxic children, which included 11 of the anoxic children with their sibling controls. Only the results from the leads of the occipital, parietal, and temporal areas are considered in the compilation of the data. Of the total anoxic children examined, 8 showed definite abnormalities of the electroencephalograph; 3 showed minimal changes, and 10 were normal. Of the 10 anoxic children with sibling controls, 4 showed definite abnormalities, whereas of the sibling controls 2 showed only minimal changes. If the definitely abnormal EEG's are considered then the results approach a significant difference at between the 10 and 5 per cent level of probability. Attention should be drawn to the fact that the psychology tests are concerned mainly with the functions of the higher centers. Organic changes in areas of the brain which do not affect reasoning or perception would not be measurable by these tests. On the other hand, the EEG with the leads used from the different areas of the skull may be more discriminating as to the possibility of organic involvement which may relatively not affect the higher functions.

Comment

In our study apneic children were those who were most severely affected in a group of over 40,000 births. One would expect that with this highly selected group (as to the severity of anoxia) the signs of dysfunction would be preponderant. That such is not the case in many of the examinations conducted by us is evident in the negative results which were obtained on many of the psychology tests, which included the Bender-Gestalt, figure completion, average intelligence quotients, illusions and ambiguous figures on an organic battery, and laterality related to the developmental history such as delayed walking, delayed talking, eneuresis, infantile speech, neuromuscular disorder, and mental retardation as far as school placement is concerned, and on neuropsychiatric disorders such as epileptiform seizures, strabismus, behavior problems, emotional disturbances, focal neurological lesions, and stammering. Our results indi-

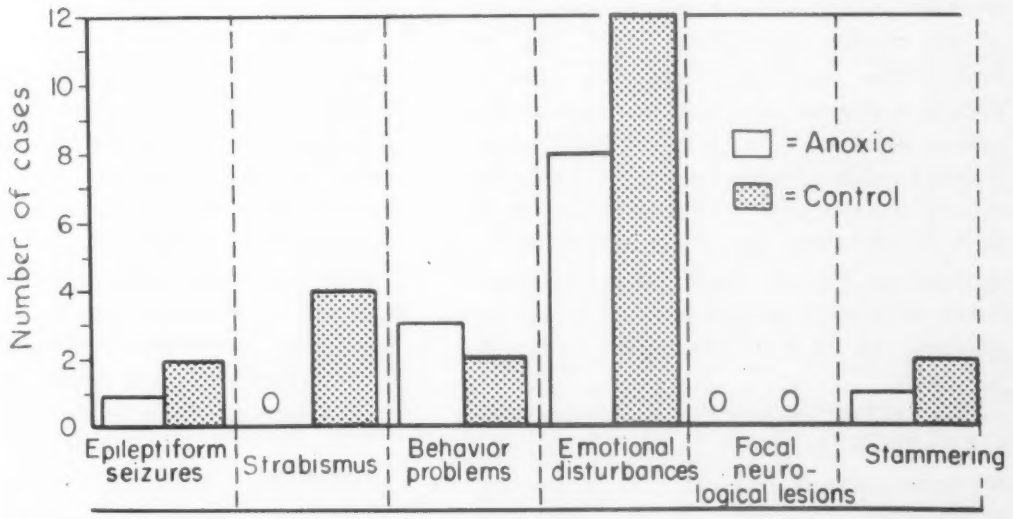

Fig. 3. Distribution of neuropsychiatric disorders.

No. of children		*No. of disorders*		*Average disorder per child*	
Anoxic	30	Anoxic	17	Anoxic	0.6
Control	54	Control	32	Control	0.6

cate that anoxia of the severity experienced by these infants affects some individuals but not others.

That such indeed appears to be true of the infants studied by us is indicated by the greater variability of the anoxic group. This means that there is a greater spread of their scores when compared with a similar group in which birth was normal. This greater variability may be due to the possibility that only a small number of cases are actually affected but not a sufficient number to produce statistical reliability when the individuals are compared as a group. That such appears to be the case is shown by the fact that a greater number of the anoxic children are feebleminded as measured by the Stanford-Binet test, with an I.Q. below 70. In the general population the frequency of this occurrence should be 3 per cent. In the anoxic group it was 20 per cent but in the controls it was 2.5 per cent, or approximately the expected number. That the I.Q. need not suffer in all of the anoxic children is shown by the fact that 10 per cent had I.Q.'s over 110, or at an above average level, but this was not true of any of the controls. This high score is especially pertinent when the fact is considered that the population which was studied fell into the so-called dull normal group and was not representative of the average population. In a similar fashion the electroencephalogram showed a definite abnormality in 27 per cent of the anoxic children examined. Of the anoxic children with sibling controls 36 per cent showed definite abnormalities but not one of the controls. Only slight irregularities were obtained in 2 of the latter group. Infantile habits are also more persistent in the anoxic children (63 per cent as compared with 26 per cent).

Our studies lead to the conclusion that a child can suffer severe anoxia without any deleterious effects, but that only in isolated instances will this result in any pathologic involvement of the brain resulting either in feeblemindedness or an abnormal electroencephalogram. These findings are unlike those of some of the more recent reports that a generalized lower proficiency can be expected as an outcome of anoxia.

The clinical statistical studies of anoxia fall into three groups, the retrospect, the prospect, and the longevity study. Each has advantages and disadvantages. The retrospective study chooses an affected population, sets up a control group made up of unaffected individuals, and compares the incidence of anoxia in each group at birth. The prospective study chooses a group of persons known to have suffered anoxia at birth, selects unaffected individuals as a control group, and compares the incidence of subsequent neuropsychiatric difficulties.

The advantage of the first method is that a large group is available for testing. The chief criticism is a lack of documented material. The information regarding birth is often taken from incomplete records or secured by maternal recall which is unreliable. The advantage of the second method is the selection of the subjects by information taken from documented records. The disadvantages are the small number of subjects tested and the difficulties in locating the patients. Criticisms common to each are disregard of factors which may have a definite bearing on deviations in development and the changes and interruptions which may occur at times in the growing organism.

The best studies are the prospective longevity studies which have documented histories recorded from periodic observation throughout the life of the individual. So far these are few in number and have never covered the entire period from birth to maturity. It is toward these developmental studies that future research must be oriented in order to obtain a definite answer as to how anoxia or other conditions related to birth affect the growth in the physical and mental spheres of the individual.

Summary

Out of a group of more than 40,000 births, children were selected who showed the most severe anoxia at birth. They were compared with a group of children with normal spontaneous delivery and spontane-

ous respiration and with their sibling controls who suffered no difficulty at birth. The ages ranged from 3 to 19 years.

Psychological, neurological, and physical examinations were conducted on the children. Data from the medical records were tabulated and a psychiatric case history obtained on each child.

The results show that severe anoxia may have deleterious effects in later life. There is a greater incidence of feeblemindedness as indicated by intelligence tests among the anoxic children (20 per cent as compared with 2.5 per cent of the controls), a greater incidence of pronounced electroencephalographic abnormalities (36 per cent in the anoxic group but none in the controls), and a greater persistence of infantile habits (63 per cent in the anoxic group and 26 per cent in the controls).

There were no differences on the Bender-Gestalt, figure completion, average intelligence quotient, illusions, ambiguous figures of the organic tests, and laterality tests, on the neurological and medical findings, on neuropsychiatric disorders such as delayed walking, delayed talking, eneuresis, infantile speech, neuromuscular disorders, and mental retardation as measured from the scholastic placement of the patient.

Not only are generalized signs of dysfunction between the two groups not consistently present, but the majority of the children in the anoxic group remain relatively unaffected by the severe birth conditions. Many of the children in the anoxic group were of superior ability.

As a consequence of the instances of relatively severe changes in some of the anoxic children, the anoxic population is more variable than a similar control group. This factor may minimize statistically significant differences when group comparisons are made. The results also contradict the reports by some investigators that anoxia produces a generalized lowering of functions in the group as a whole rather than producing deleterious effects in isolated instances.

Special appreciation is expressed to Eleanor M. Jantz, Walter Stephens, and Richard H. Walters, for conducting the psychological tests and for some of the statistical analyses of the data.

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Discussion

Dr. Douglas Buchanan, Chicago, Illinois. A discussion in an obstetrical society of the late effects on a child of anoxia during birth should start with the recognition of Dr. W. J. Little, for it was he who introduced this idea to medicine. His classic paper to the London Obstetrical Society in 1862 had as its title, "On the Influence of Abnormal Parturition, Difficult Labours, Premature Birth, and Asphyxia Neonatorum, on the Mental and Physical Condition of the Child, Especially in Relation to Deformities." He said that the object of the communication was "to show that the act of birth does occasionally imprint upon the nervous and muscular systems of the nascent infantile organism very serious and peculiar evils." Until that time it was assumed that if an infant survived even the most prolonged or arduous delivery had no permanent effect upon him. Indeed the president of the Obstetrical Society of London said that he had difficulty in discussing Dr. Little's paper because of the entire novelty and originality of the subject. This now seems strange to us especially since Shakespeare described this subject in the opening lines of Richard III

> I, that am curtail'd of this fair proportion,
> Cheated of feature by dissembling nature,
> Deform'd, unfinisht, sent before my time
> Into this breathing world, scarce half made up,
> And that so lamely and unfashionable
> That dogs bark at me as I halt by them.

Types of spasticity and of weakness and degrees of mental retardation were, of course, well

known at that time, but, since they were so often not revealed or recognized until some months after birth, the possible relationship of difficulty in delivery was not understood.

During the last century the pathogenesis of spasticity and of mental retardation has been widely studied. Sarah McNutt in 1885 and Herbert Spencer in 1892 regarded injury at birth as the most common cause. Freud in 1897 and Collier in 1899 believed prenatal defects in development of the nervous system to be most often the basis of these abnormalities. Studies such as these continue to be made.

The authors of the paper under discussion here have approached the problem from another aspect. They studied and followed the intellectual development of a number of infants who had anoxia at birth. They report no real defect in development of these children. This result, although unquestioned, was probably as unexpected to the authors as to us. It must not be assumed, however, that anoxia at birth is always or even usually so benign. It is still true that many children with spasticity or mental retardation have as the basic pathogenesis natal cyanosis, asphyxia, or anoxia.

Dr. William Tomlinson, Chicago, Illinois. The main point of this paper, as far as I am concerned, is that only some children who are anoxic suffer any permanent damage. Of course, the crucial question is "Why is this so?"

There is all the difference in the world in the statement "Anoxia *is* detrimental to an infant" and the statement "Anoxia *can be* detrimental to an infant." I believe this study makes a convincing point of this difference. The specific question raised again in this study is: Why do certain children suffer deleterious effects from anoxia while others do not? What are the other pertinent factors, and how can they be studied? The answer to this and many other questions may be found when we learn more about differences in metabolism between different species, and, more important, about the differences between individuals in the same species.

Being only about 100 years old, biochemistry is still in its infancy, and its methods are crude. We shall no doubt have to learn to measure and study enzymes that are not now even known to exist. We shall have to learn more about the effects of temperature on brain metabolism. We shall have to study the important day-to-day variations in oxygen requirements of various parts of the brain in the first few weeks of life. As Barcroft wrote shortly before he died, in regard to the initiation of breathing in babies, "A lifetime might be spent in filling in the details." This is certainly an understatement.

One other practical problem raised in a study of this type is that of getting good neurological evaluations early in life. Pediatricians have often felt neglected by neurologists who may seem unable to get interested in small babies. Psychologists, even at the post-Ph.D. level, may have had little experience with small children or with brain-damaged children. When we further develop our methods of clinical evaluation and our understanding of metabolic processes, we shall have more *facts*. When we have more facts, we can alter our theories accordingly.

Dr. Charles E. Galloway, Chicago, Illinois. It seems to me that the children whose cases you have reviewed are still children and you are trying to evaluate their mental capacity as children. I hope that you will keep these statistics and these names in mind and 20 or 25 years from now you will tell us how they are as adults. When this idea reappeared 10 or 15 years ago I began to go over the records. I selected the records of children whom I knew had been slow breathers and had a hard time living. I tried to find out how many of these children came out all right. Some became presidents of their classes and Phi Beta Kappas. I became so discouraged that I did not see how I could prove anything.

The question I would like to ask is, "Can an individual's intelligence quotient change." I think it shows marked change when the youngster gets fired with ambition to do something and has opportunities of doing it.

Dr. Benaron (Closing). With regard to Dr. Galloway's question as to whether or not these children were examined at a later date, I thought I stated that the age range was 3 to 19 years.

Dr. Yacorzynski (Closing). The question as to whether the intelligence quotient can change can be discussed at some length but I would like to answer it by two statements.

1. In the first place, in isolated instances the intelligence quotient can change. Intelligence is affected both by emotional factors and by organic conditions which may involve the brain. In some

instances emotional factors may depress the results on an intelligence test thus decreasing the score. This can obviously also happen in the opposite direction. Organic involvement of the brain occurring later in life may obviously also change an individual's intelligence quotient.

2. In the second place, in most individuals the intelligence quotient will not show an appreciable shift. The probability of this occurring in a group of individuals of the size that we used in this study is very slight indeed. Consequently, one has little reason to believe that in studying a group of individuals any significant changes will occur in the intelligence quotient due to other factors than that introduced by the experimental variable.

Experiences in the diagnosis of fetal life with the fetal electrocardiogram

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DIAGNOSTIC information about the existence of fetal life is an area of potential usefulness for fetal electrocardiographic technique. Increased interest has been shown in direct recording and presentation of the fetal electrocardiogram, as well as in indirect presentation of heart rate information.[1-4] The latter studies represent an effort to extract diagnostic information from the observed pattern of heart rate variation.[5, 6] In direct fetal electrocardiographic studies, it has been shown that the fetal electrocardiogram is demonstrable as early as 11½ weeks of embryological age, and that certain types of congenital cardiac malformation are demonstrable antenatally.[1] It has been shown that the diagnosis of multiple pregnancy may be made as early as 16 weeks with the fetal ECG.[2] The possibilities for the diagnosis of fetal life have received attention and require further documentation and analysis. In this report, a series of instances will be presented in which the fetal electrocardiographic technique was used for the purpose of assessing the existence of fetal life.

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This research was supported by a grant-in-aid from the United States Public Health Service, RG-4462.

Materials and methods

Our studies of the fetal ECG have now encompassed 600 instances in 517 subjects. During these studies, specific requests for the diagnosis of fetal life, when fetal heart tones could not be heard, were received in 25 cases. These cases are the basis for this report. The techniques for the recording of the fetal electrocardiogram have been reported previously.

Case reports

Case 501 (T. B.). This patient, gravida iii, para 0, was reported bleeding, at 20 weeks of pregnancy, with uterine contractions. Fetal heart tones could not be heard. The physician considered operative intervention because of an incompetent cervix, but desisted because fetal life could not be demonstrated. A fetal ECG was requested and obtained. It was positive. Operation was performed, and the contractions stopped, but the operation was not successful in that the patient aborted about 3 weeks later. The fetal ECG as indicated in Fig. 1 showed a clear positive, answering the question of fetal life in the affirmative.

Case 502 (S. C.). This mother, a gravida iii, para ii, was about 5 months pregnant by date, but uterine size was smaller than expected. There had been slight bleeding. Fetal heart tones could not be heard. A fetal ECG was negative. The patient went into labor two days later and was delivered of a 4 months' macerated fetus. In this instance, the fetal ECG supported the clinical impression of fetal death.

Case 503 (M. R. B.). There was a history in

this case of 3 previous molar pregnancies, terminating in the early months. Uterine enlargement was greater than in the previous instances. A fetal ECG was negative. The patient went into labor shortly thereafter and spontaneously passed a mole, at 18 weeks.

Case 504 (H. B.). This gravida i, para 0, had had severe diabetes since age 7 years. She was maintained on 50 units U-80 NPH insulin. There was mild pitting edema during pregnancy, and at 4 weeks before term she developed 4-plus edema and experienced some rise in blood pressure. Fetal heart tones had been heard 3 days earlier, but on the morning of the fetal ECG no fetal heart tones could be heard. The fetal ECG was negative. Labor was induced and the patient was delivered of a stillborn infant, which was moderately macerated.

Case 505 (M. K.). This 20-year-old mother was in the hospital at 5 months, with moderately severe bleeding and mild contractions. No fetal heart tones could be heard at this time. The key question for management of this case was whether the fetus was still alive. The fetal ECG proved to be positive. Every effort was made to maintain the pregnancy. At her second admission 2 weeks later, she passed a 250 gram fetus. Sections of the cord showed congenital absence of one umbilical artery. There was extensive hemorrhage and necrosis of the placenta.

Case 506 (B. D.). A 28-year-old mother, weighing 249 pounds, was in labor 13 hours, with ruptured membranes for 10 hours, with very little progress, when the fetal heart tones disappeared. The patient had pre-eclamptic toxemia and there was some cephalopelvic disproportion. A fetal ECG showed definite fetal complexes (Fig. 2). On the basis of the cephalopelvic disproportion with a viable infant by fetal ECG, a low cervical cesarean section was decided upon and performed. ". . . the infant was limp, obviously depressed, however reflexes were present and there was spontaneous movement. The baby was resuscitated with a tracheal catheter and bulb syringe. Respirations were established approximately 2 minutes after delivery. The cry was improved. Respiration was improved." On the sixth postpartum day, ". . . baby excellent, eats very well." Mother doing well.

Case 507 (J. M. T.). A 23-year-old gravida ii, para i, hospitalized at 20 weeks of pregnancy, was bleeding slightly. The fetal heart tones could not be heard. A fetal ECG was positive. All efforts were bent toward preserving the pregnancy. Fig. 3 shows the ease with which the diagnosis of fetal life could be made in this case.

Case 508 (B. G.). This patient, gravida i, para 0, had moderately severe pre-eclampsia, with long-standing renal disease. Under treatment with antihypertensive drugs the blood pressure was controlled, but the fetal heart tones became slow and irregular, and then disappeared. Fetal ECG showed definite fetal complexes, but with the rate going down to 90. Premature labor occurred one week later, with delivery of a stillborn infant. The fetal ECG in this instance was a more sensitive indicator of the state of fetal life than was auscultation.

Case 509 (H. S.). This patient, gravida vi, para iv, had had 1 abortion. She entered the hospital at 20 weeks because of hemorrhage. No fetal heart tones could be heard, although they were heard 2 weeks previously. The patient had been treated for postural hypertension syndrome 4 weeks earlier. A fetal ECG was negative. One week later the patient was delivered of a stillborn male infant. In view of the great probability of a positive fetal ECG at 20 weeks with a living fetus, a negative fetal ECG at this time at least would support the concept of intrauterine death.

Case 510 (J. K.). In this instance, a diabetic woman, gravida iii, para ii, entered the hospital at 27 weeks of pregnancy with bleeding and presumed loss of fetal life. No fetal heart tones could be heard. A fetal ECG was positive (Fig. 4). Hence, management of the case was toward preservation of the pregnancy. The decisive information was provided by the fetal ECG.

Case 511 (J. M.). A gravida iv, para ii, who had had 1 abortion, entered the hospital with much bleeding at 24 weeks of pregnancy. The expected date of confinement was not known with any degree of precision because of a stillbirth the previous year and no menstrual periods since. No fetal heart tones could be heard. The fetal ECG was positive, the fetal heart rate was steady at 156 (Fig. 5). In this instance, as in the similar cases, management of the patient was directed toward the maintenance of the pregnancy and serial follow-up fetal electrocardiograms were planned to help to indicate the course of treatment.

Case 512 (P. E.). This 34-year-old patient entered the hospital with reported vaginal bleeding for 5 days. She was presumed to be at 24 weeks, although there was some doubt about the

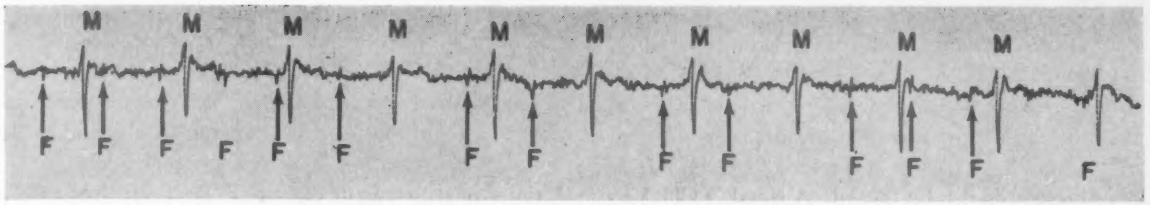


Fig. 1. Positive fetal electrocardiogram in an instance when fetal heart tones could not be heard. Twenty-week pregnancy, with bleeding.

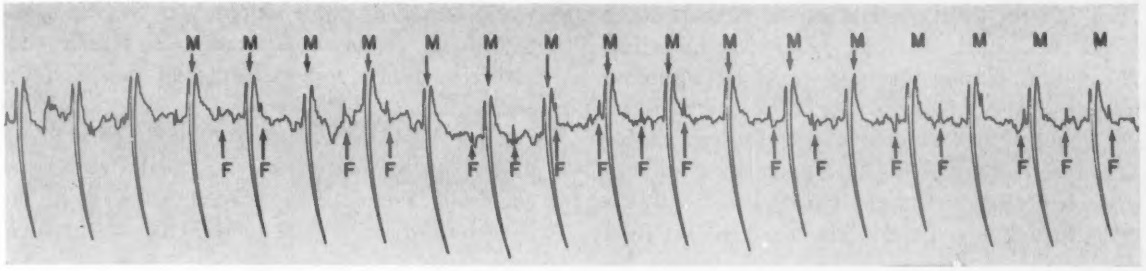
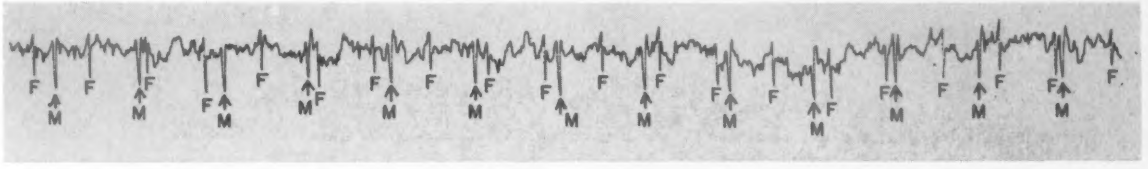


Fig. 2. Positive fetal electrocardiogram in an obese mother (249 pounds) where fetal heart tones could not be heard. Pre-eclamptic toxemia with cephalopelvic disproportion.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pregnancy. No fetal heart tones could be heard. Fetal ECG was negative.

Case 513 (F. R.). A 22-year-old gravida ii, para i, entered the hospital with contractions, bleeding and threatened premature delivery at an estimated 20 weeks gestational age. No fetal heart tones could be heard. A fetal ECG was positive (Fig. 6). Efforts were directed toward maintenance of the pregnancy.

Case 514 (R. L.). The patient was a gravida iii, para ii, at 34 weeks. No fetal movement had been felt for 10 days, and no fetal heart tones could be heard. A fetal ECG was negative. X-ray examination about 2 weeks later showed irregularity and overlapping of the fetal skull bones suggestive of fetal death. Labor was induced with the delivery of a macerated stillborn male fetus. Intrauterine death occurred 4 weeks prior to delivery. In this case the negative fetal ECG supported and was consistent with the clinical impression and final outcome.

Case 515 (L. M.). This patient, gravida ii, para 0, had had 1 abortion. She was at 33 weeks of pregnancy and gave a history of grand mal. Fetal heart tones had not been heard to the date of the recording. The fetal electrocardiographic record was "noisy" and it was difficult to identify fetal complexes with any certainty, so that the record should be classed as negative. This was an example of a false-negative at 33 weeks, since a viable infant was delivered, although a cephalohematoma was present, together with a questionable facial palsy on the right.

Case 516 (L. K.). A gravida i, para 0, reported for a fetal ECG. No fetal heart tones could be heard, and pregnancy was at the twenty-third week. The fetal ECG was positive.

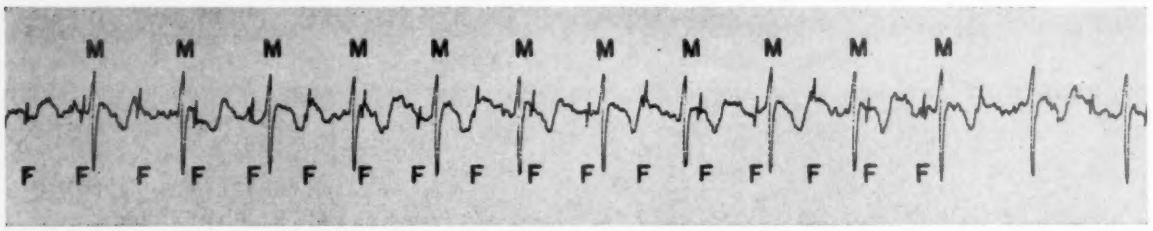

Fig. 6. Twenty weeks' gestation; contractions and bleeding; threatened premature delivery. No fetal heart tones heard. Fetal electrocardiogram was positive.

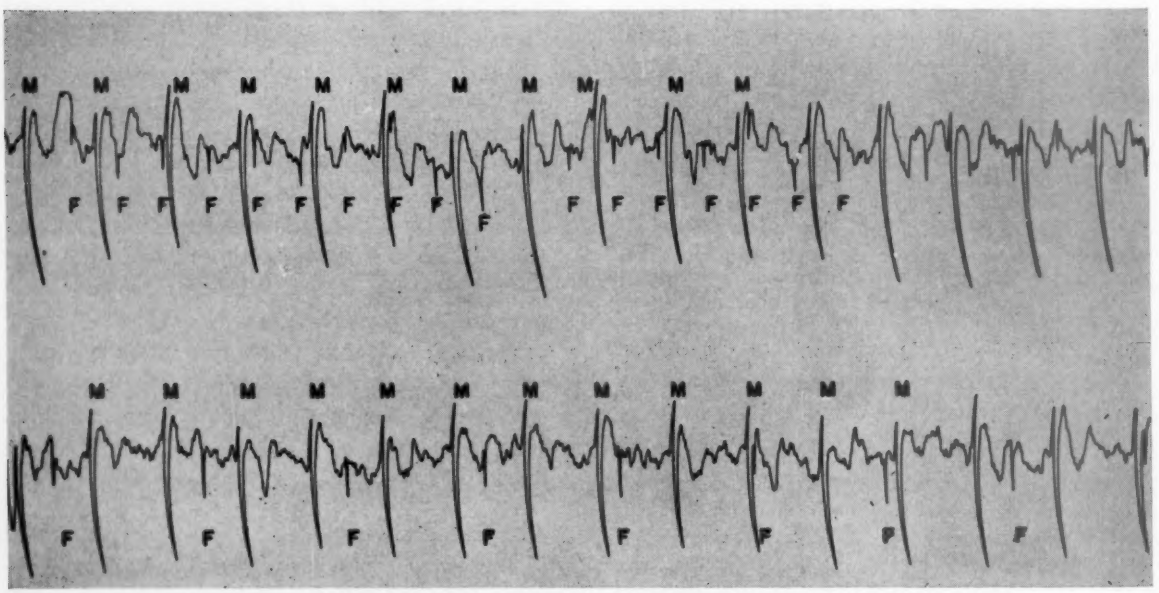

Fig. 7. Clear, positive fetal electrocardiogram at 17 weeks. Intermittent bleeding, occasional cramping. No fetal heart tones heard. Lower tracing in same case shows profound bradycardia.

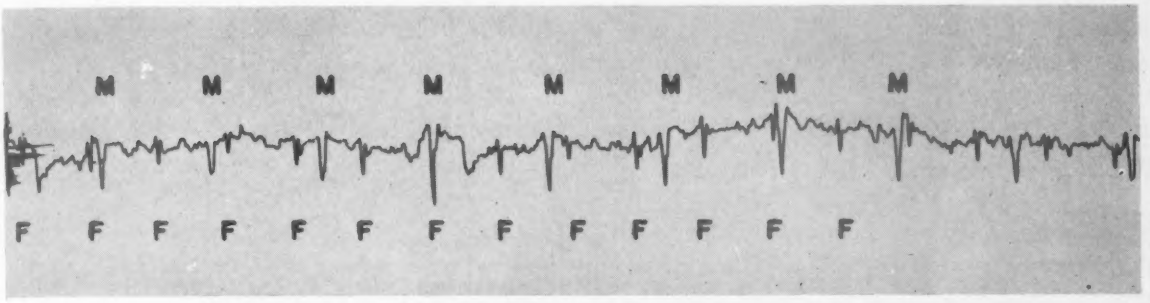

Fig. 8. Clear, positive fetal electrocardiogram in a patient with uncontrolled diabetes, weight 261 pounds. No fetal heart tones heard. Diagnosis in this instance made in one tenth of a second.

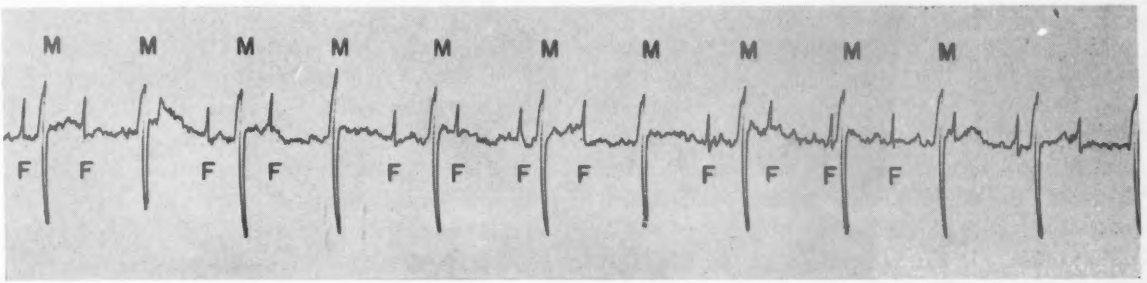

Fig. 9. Positive fetal electrocardiogram in a case of difficult labor and a face presentation, where fetal heart tones disappeared. ST segment depression in this instance suggested an unfavorable fetal environment.

Case 517 (H. H.). This gravida i, para 0, reported for a fetal ECG when 16 weeks pregnant. She had been bleeding for 3 weeks, but did not feel life; possibly she had miscarried. The fetal ECG was positive, and the fetal heart rate was 156. This was an example of early and useful information for the physician.

Case 518 (J. B.). In this case, a 25-year-old patient, gravida v, para 0, who had had 5 abortions, was admitted at 17 weeks of pregnancy with intermittent bleeding and occasional cramping. No fetal heart tones could be heard. A fetal ECG was requested and done, and showed a clear positive, as indicated in Fig. 7. Two weeks later, the mother passed a 14½ ounce, 10 inch female fetus, which was breathing and actively moving. It survived for a few hours. Fig. 7 showed two significant records which provided useful information. The upper tracing shows how clear a fetal ECG can be at early weeks of gestation, even when the fetal heart tones cannot be heard. The lower tracing shows a transient episode of profound bradycardia, with the fetal heart rate dropping to 48. In other portions of the tracing there is evidence of a lesser transient bradycardia. The mechanism of such pronounced bradycardia at this time is under investigation.

Case 519 (R. N.). In this instance, a diabetic mother was being followed through pregnancy with serial fetal electrocardiograms. All had been consistently positive, and had shown no morphological change or remarkable rate change. At the thirty-eighth week, a fetal ECG was negative, and fetal complexes could not be identified. A repeat fetal ECG 2 days later was positive. A viable infant was delivered by cesarean section. For the present, not enough information is available to explain such negative findings. Hence, they must be treated with caution. The best policy, as indicated, is a repeat fetal ECG a few days later. In view of the appearance of such occasional false-negatives, a negative fetal ECG may have no meaning.

Case 520 (J. D.). This mother, a gravida v, para iii, who had had 1 abortion and 1 stillbirth, had uncontrolled diabetes. She had no living children. She weighed 261 pounds when she entered the hospital at term. No fetal heart tones could be heard. Fetal ECG was requested and done. As may be seen from Fig. 8, the fetal electrocardiogram was an easily diagnosed positive.

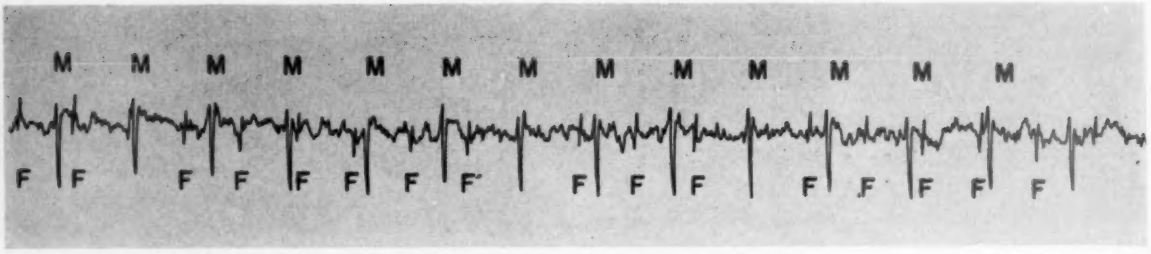

Fig. 10. A 5 months' pregnancy, vaginal hemorrhage, where no fetal heart tones could be heard. Fetal electrocardiogram was positive.

The diagnosis in this instance may be made in one tenth of a second, i.e., the time necessary for one fetal complex to appear after the paper drive is turned on. The fact that the fetal electrocardiogram can be recorded in this instance of obesity is of great significance. The information indicating a viable infant was enough to support a decision for cesarean section, but the patient went into active labor and was delivered at once. A viable female infant, weighing 8 pounds, 11 ounces, was born.

Case 521 (J. E.). A gravida vi, para v, was at term. She had had a difficult prolonged labor and a face presentation. Fetal heart tones disappeared during labor. A fetal ECG was requested, and was positive, as indicated in Fig. 9. In this instance also, the diagnosis is made in a fraction of a second. This indication of a viable fetus was helpful in the decision for a cesarean section. Successful delivery of a living infant resulted. The fetal ECG shows some ST segment depression, suggesting an unfavorable fetal environment.

Case 522 (E. T.). This gravida i, para 0, was seen at 5 months of pregnancy with vaginal hemorrhage. No fetal heart tones were heard. The fetal ECG was positive, providing useful information for the management of this patient (Fig. 10).

Case 523 (T. E.). This mother entered at 25 weeks, with vaginal bleeding. No fetal heart tones could be heard, and no life had been felt by mother. Fetal ECG was positive (Fig. 11).

Case 524 (S. H.). Subject came in at 7 months, having had a traumatic fracture of the skull (pistol whipped). No fetal heart tones were heard, and no fetal movement could be felt. The fetal ECG was negative. Nine days later, she was delivered of a macerated stillborn infant.

Case 525 (B. L.). A gravida ii, para i, was seen at 17 weeks, with hemorrhage, and a hard, tender uterus. No fetal heart tones were heard. Fetal ECG was positive. Two follow-up fetal electrocardiograms were also positive.

Comment

In the work of other investigators, efforts have been made on occasion to estimate the accuracy of the fetal electrocardiogram, as well as the possibilities for the diagnosis of fetal life, without regard to the epoch of gestation. In our opinion, it will be much more helpful to take into account the varying accuracy of fetal electrocardiographic technique at various epochs of gestation. In another report from this laboratory, it was shown that a high percentage of positive fetal electrocardiograms is recorded from the eighteenth week to the twenty-fourth week; that an epoch of reduced accuracy ensues, to the thirty-second week, and that thereafter accuracy increases, to term. The diagnosis of

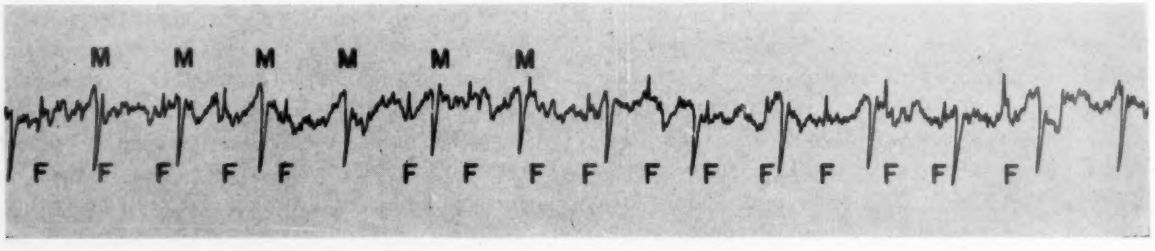

Fig. 11. A 25 weeks' pregnancy, vaginal bleeding, no fetal heart tones heard, no life felt by mother. Fetal electrocardiogram was positive.

fetal life needs to be discussed in specific relationship to these epochs.

Prior to the eighteenth week, there is only moderate accuracy with fetal electrocardiographic technique (about 40 per cent at 15 weeks, for instance). Hence, in any effort to diagnose fetal life at this time, a negative fetal ECG has no significance. The positive fetal electrocardiograms as seen are certain, of course, and only these should be used. Four of the cases in this series fall into this group, Cases 503, 525, 517, and 518. Of these, 3 were positive and require no further comment beyond the obvious usefulness of the information. One negative was in an instance of a mole delivery.

From the eighteenth through the twenty-fourth week, a high accuracy in recording the fetal electrocardiogram is to be expected. Hence, not only are positive findings certain, but a negative fetal ECG in this epoch should raise at least the possibility of the absence of fetal life. This should be done with caution, since 2 or 3 per cent of false-negatives are seen. Repeat recording is desirable. Eleven of our cases fall into this epoch. Eight were positives and were helpful in establishing the diagnosis. There were 3 negatives, Cases 502, 509, and 512. Of these, one patient was delivered of a macerated fetus, one was delivered of a stillborn infant with slight maceration, and the third had pseudocyesis.

During the epoch of reduced accuracy from the twenty-fifth through the thirty-third week, only positive findings should be utilized. A negative finding has little or no meaning, since the accuracy drops to about 50 per cent. Repeat recording is suggested. In this series, we have only a few cases. Two instances were positives. One case was a negative and a macerated stillbirth was the outcome. The last case, 515, was a false-negative, since a viable infant was delivered.

With the increased accuracy toward term, high proportions of positives are seen, and increased reliance can be placed upon the fetal ECG. It should be remembered that 3 per cent false-negatives are seen. In the series presented, we had 6 cases (504, 506, 514, 519, 520, and 521). Of these, 3 were positives, and 3 were negatives. In one negative, there was delivery of a macerated fetus; in a second negative, there was death in utero. The third negative was a false-negative, since a repeat fetal electrocardiogram the following day was positive.

In the instances presented in this report, it is shown that fetal electrocardiography can be most helpful. The data indicate that in early pregnancy (15 to 25 weeks) the absence of fetal heart tones plus the presence of bleeding is insufficient, probably, to justify the presumption of the loss of fetal life. An effort to record the fetal electrocardiogram is mandatory. When, in such instances, the fetal electrocardiogram is positive, the presence of fetal life is certain. Negatives should be treated with caution.

It is of considerable interest to note that in at least 2 of the cases presented, there was great maternal obesity. Yet is was possible to demonstrate a positive fetal electrocardiogram, occasionally with great ease. Obesity per se is not necessarily a barrier to the recording of the fetal electrocardiogram. In this may lie another of the important contributions of this technique.

Summary

1. Twenty-five instances in which the technique of fetal electrocardiography was used for the diagnosis of fetal life, because fetal heart tones could not be heard, are presented and discussed.

2. It was shown that the positive fetal electrocardiograms which could be expected in a number of these instances were evidence for the existence of fetal life.

3. The significance of negative findings is discussed. It is suggested that the negative fetal ECG has no meaning prior to 18 weeks, and in the epoch of low accuracy from the twenty-fifth to the thirty-second week.

4. In the epochs of high accuracy from the eighteenth to the twenty-fourth week, and again toward term, a negative fetal ECG can raise a presumption as to the absence of fetal life. Even at these times, however, there are about 3 per cent false-negatives.

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Electroencephalographic studies in anencephalics

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PREVIOUS studies have established a uniform pattern of the electroencephalogram obtained from the brain of fetuses or newborn infants when the individual is subjected to metabolic stress.[1, 2] The present work was initiated to correlate the abnormal tracings with histologic evidence of this condition. Anencephalic monsters were examined following delivery. Three infants were so tested and, following death, the brains were available for histologic study. The details of these studies follow.

Case reports

Case 1. R. P., a 26-year-old white woman, gravida iii, para ii, was 37 weeks pregnant; the present pregnancy was complicated by polyhydramnios. The membranes were artificially ruptured and labor initiated. A full-term female anencephalic infant was delivered.

Previous pregnancies were uncomplicated and resulted in the delivery of living healthy infants.

The general health of both parents is good. The mother had surgical correction of cleft palate and harelip as an infant.

Case 2. E. K., a 24-year-old white woman, gravida i, para 0, had been unable to conceive for 6 years apparently due to her husband's oligospermia. Subsequent to his treatment by several urologists, conception occurred. Pregnancy progressed satisfactorily until the seventh lunar month when the rapid enlargement of the uterus was observed. This enlargement continued until time of delivery. Roentgen examination late in pregnancy demonstrated the presence of an anencephalic infant. A full-term moribund female infant was delivered by low forceps under light nitrous oxide–oxygen anesthesia.

The general health of both parents is good. Family history is noncontributory.

Case 3. C. M., a 25-year-old white woman, gravida i, para 0, was at term. The pregnancy was uncomplicated and the diagnosis was fortuitous when roentgen studies were made to determine presentation of the fetus. Labor occurred spontaneously and a moribund male anencephalic infant was delivered.

The parents are in good health. Family history is noncontributory.

Description of anencephalic monsters.

R. P. The face was oval in shape; the nose, lips, and ears were well-developed; bilateral exophthalmos was present. The head was flattened anteroposteriorly. The frontal, temporal, parietal, and occipital bones appeared partially developed. Protruding from the open cranial vault was a mass (6 by 6 by 2½ cm.) which was grossly divisable into two parts, anterior and posterior. The entire mass was covered by a fine arachnoid membrane. Gyri and sulci were not evident. The anterior portion was soft and was lobulated and grossly resembled cerebellum. The forepart was blue and the remainder, red. The posterior portion of the protruding mass was soft and red. After removal of the "brain" (protruding mass), inspection of the cranial cavity revealed a slitlike anterior fossa but no middle or posterior fossa. There was no associated spina bifida.

TYPE. Median meroacrania (podencephalus).

E. K. The face and its external features were similar to the previous infant. The head was flattened anteroposteriorly. The frontal, temporal, parietal, and occipital bones were partially developed. The protruding brain tissue measured 5½ by 3½ by 1½ cm. The tissue was

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covered by a fine arachnoid membrane. It was blue and homogeneous in appearance. No gyri or sulci were present. The cranial vault contained a small anterior fossa with no middle or posterior fossa. There was associated complete spina bifida.

TYPE. Median meroacrania (podencephalus).

C. M. The cranial vault was absent, revealing the brain substance to be covered by a thin grayish blue membrane. The frontal bones were present only to the supraorbital ridge. The parietal bones appeared to be entirely absent. The anterior cranial fossa was shortened. The sella turcica was flattened and the pituitary gland could not be identified. A portion of the occipital bones were present. The cerebral hemispheres consisted of a soft red-purple mass measuring 6½ by 5 by 1 cm. No cerebellum, ventricular spaces were identified. There was no associated spina bifida.

TYPE. Anteromedian meroacrania.

Microscopic examination. Microscopic examination of all specimens revealed tissue which was composed largely of thin-walled vascular spaces distended with blood and separated by small irregular masses of brain tissue. There were also large empty cystic areas which were lined by a single layer of flattened cuboidal cells. Occasionally on the walls of these cystic areas was seen a papillary structure resembling the choroid plexus. One portion of the brain tissue was lined peripherally by a thin layer of squamous epithelium.

Electroencephalograms.

Procedure. Silver electrodes were placed on the surface of the "brain" mass. They were spaced uniformly over the entire area. After a suitable period, needle electrodes were placed into the substance of the "brain" mass to a depth of 1 cm. until the conclusion of the electroencephalogram.

E. K. Initially (5 minutes after birth) waves of 1 to 3 per second of moderate voltage were recorded from the posterior (chiefly to the left) portion. Electrocardiogram was evident at 42 per minute. Continued observation revealed slowing of the waves (½ to 1 per second) but maintenance of voltage (8 minutes after birth), then progressive diminution of voltage with persistence of the slow rhythm was noticed. Occasional intermittent bursts of paroxysmal rebound activity of moderate voltage slow waves appeared, followed by almost complete absence of electrical discharges. This phenomenon was observed for 12 minutes (17 minutes after birth) after which electrical activity disappeared.

R. P. Essentially, the tracings demonstrated the same paroxysmal type of rebound electrical activity described in E. K. The paroxysms appeared at less frequent intervals. Periods of greatly diminished activity were observed during the period of observation (2½ days) prior to the death of the infant. The infant survived a period of time which permitted both sound and light stimulation. No effect was seen from either stimulus. Vaschide and Vurpas[3] reported no apparent effect from loud sounds or bright lights on an anencephalic infant that lived 39 hours. The electroencephalogram was in evidence chiefly from a small area (right parietal) of the protruding tissue ("brain").

C. M. In general, the tracing was similar to that obtained in the other 2 cases. The initial voltage ranged from 20 to 150 μv with a dominant rhythm of 0.5 to 2 per second. There was a gradual decrease in voltage with paroxsymal bursts of high voltage slow waves on two occasions. All electroencephalographic activity was absent 35 minutes after birth.

The electrocardiogram was slow (30 per minute) and irregular when recorded initially. Within 16 minutes it was absent.

Correlation of the areas of electroencephalographic activity with the histologic areas of cortical cell concentration was observed in all cases. The anoxic changes (granularity of chromatin of nucleus with deepening of staining, clumping of cytoplasm) were similarly correlated with changes in the electroencephalogram.

Comment

We have concluded from previous studies conducted on fetuses that the "immature" brain responds by a uniform pattern to oxygen want. This response has been observed in the very young fetus and in the full-term infant. It is present in both intrauterine and extrauterine existence. The mechanism of "death" as reflected in the electrical activity of the fetal brain is demonstrated as progressive slowing and loss of voltage. Interspersed with this activity is paroxysmal high to moderate voltage slow waves. This finding has been consistently observed in fetuses and now in anencephalic monsters. In two instances, rapid death ensued; in the other infant, existence was prolonged for 2½ days.

The changes in the electroencephalogram ascribed to anoxia were correlated with pathologic changes in the cortical cells attributed to the same cause.

The electroencephalographic and histologic studies reported herein provided the opportunity to observe this phenomenon on a cellular level rather than on a tissue or gross level. The area of the anencephalic brain showing these changes exhibited histologic changes secondary to anoxia.

Conclusion

1. Electroencephalograms of 3 anencephalic infants are presented.

2. Anoxic changes are described in the electroencephalograms which consist of gradual loss of voltage with slowing of the rhythm and the paroxysmal appearance of moderate to high voltage slow waves.

3. The histologic evidences of anoxia are correlated with areas of the "brain" demonstrating the electroencephalographic changes.

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Isotope localization of the placenta in suspected cases of placenta previa

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THE conservative management of placenta previa during the past few years has resulted in a substantial decrease in perinatal deaths that were attributed to premature delivery and resultant immaturity.[1-3] This objective has been accomplished by allowing most patients to proceed in their pregnancy to as close to the thirty-eighth week of gestation as possible before actively interfering by vaginal examination to determine the presence of a low-lying placenta or placenta previa. This policy of expectant treatment is based on the observation that the initial hemorrhage and subsequent bleeding episodes in placenta previa are seldom severe provided intracervical examination has not been performed and the maternal hemoglobin is at a normal level prior to the onset of the hemorrhage.[4-6]

A high degree of accuracy in the selection of patients for the conservative treatment of placenta previa would eliminate the need for prolonged hospitalization of the patient subsequently discovered not to have the entity, as well as decrease substantially the increased cost involved. Also, the apprehension and emotional stress suffered by the patient under such trying circumstances could be entirely eradicated.

A definite diagnosis of placenta previa is usually established by intracervical digital examination of the lower uterine segment. This may produce excessive hemorrhage necessitating immediate definitive therapy and, therefore, is ill advised until the fetus has reached a more mature state. Because of the dangers involved, we believe the intracervical examination should be restricted to its use in the operating room where a surgical team is ready, an infusion running, and blood available.

Direct or indirect roentgen placentography has been reported to be as high as 95 per cent accurate.[7] However, there are certain disadvantages associated with this procedure. The special techniques of radiographic placentography are somewhat difficult to master. We are unable to produce consistently films of sufficient quality to localize the placental site with any degree of accuracy. There is considerable movement and manipulation of the patient, and most films require interpretation by an experienced radiologist usually not present during an emergency.

The major disadvantage appears to be related to possible radiation damage to the patient's ovaries and to the unborn fetus. Accumulating evidence on the genetic effects of radiation is quite disturbing.[8] Rugh[9]

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Presented at the Fifth Armed Forces Obstetrics and Gynecology Seminar, U. S. Naval Hospital, Portsmouth, Virginia, Oct. 26, 1959, and at the Sixth Annual Meeting District VIII of the American College of Obstetricians and Gynecologists, Honolulu, Hawaii, Nov. 18, 1959.

This work is not to be construed as representing the views of the Department of the Navy.

states that the damaging effects of ionizing radiation become more subtle with advancing fetal age and may well produce viable but psychologically ill-adjusted individuals. Investigations by Stewart and associates[10] suggest that, besides causing genetic damage, diagnostic radiographic procedures in the prenatal period may cause a higher incidence of leukemia or cancer in the subsequently born child. With the accumulation of this alarming evidence, the obstetrician should make every effort to keep radiation exposure of pregnant patients to an irreducible minimum in all indicated procedures.

Because of the manifest disadvantages associated with radiographic placentography, placental localization by radioisotopes was evaluated to determine its reliability and safety. Isotope placentography was first reported by Browne[11, 12] in 1951 and 1952. Because the placenta is essentially a pool of blood in the gravid uterus and therefore represents a local accumulation of the radioactive isotope, it can be localized by means of this technique. Browne used radioactive sodium to localize the placenta for research purposes. He suggested that this method might be applicable in the clinical diagnosis of placenta previa. This procedure was confirmed in this country by Weinberg and associates.[13] The radioactive sodium diffused rapidly out of the vascular system and the measurements had to be completed within a few minutes after the injection, and they were rarely reproducible. Because of these limitations, these investigators introduced the use of radioiodinated human serum albumin to further increase the accuracy and safety of this procedure. Hutchinson, Bennett, and Gean[14] made certain modifications in this technique and interpretation. They studied 30 patients and were able to correctly localize the placenta in all cases in which it was implanted in the lower uterine segment.

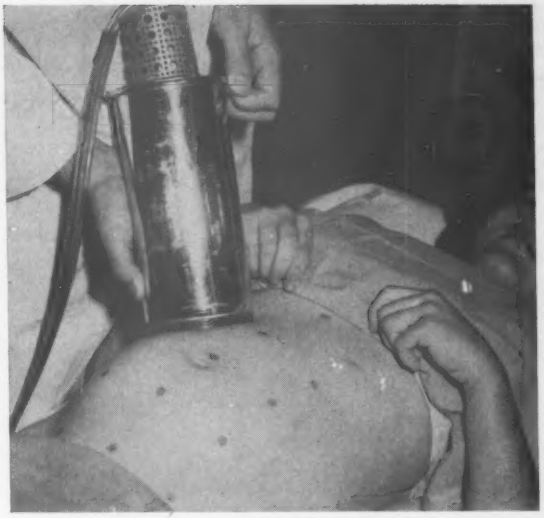

Fig. 2. Picture demonstrating the reference point (xyphoid) and the 12 sections over the gravid uterus which are counted with the scintillation counter. (Official photograph, U. S. Navy.)

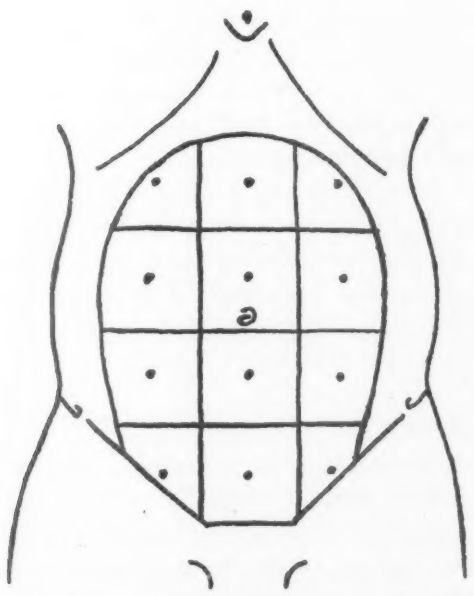

Fig. 1. Illustration of sections of the abdomen over the gravid uterus which are counted with the scintillation counter.

A summation of our experience with the isotope technique in localizing the placenta and a report of our results to date provide the basis of this presentation. Certain modifications in the original technique and interpretation of results as described by Hutchinson and co-workers[14] were carried out in our study. Only those patients who were admitted to our obstetrical service for third trimester bleeding or for elective repeat

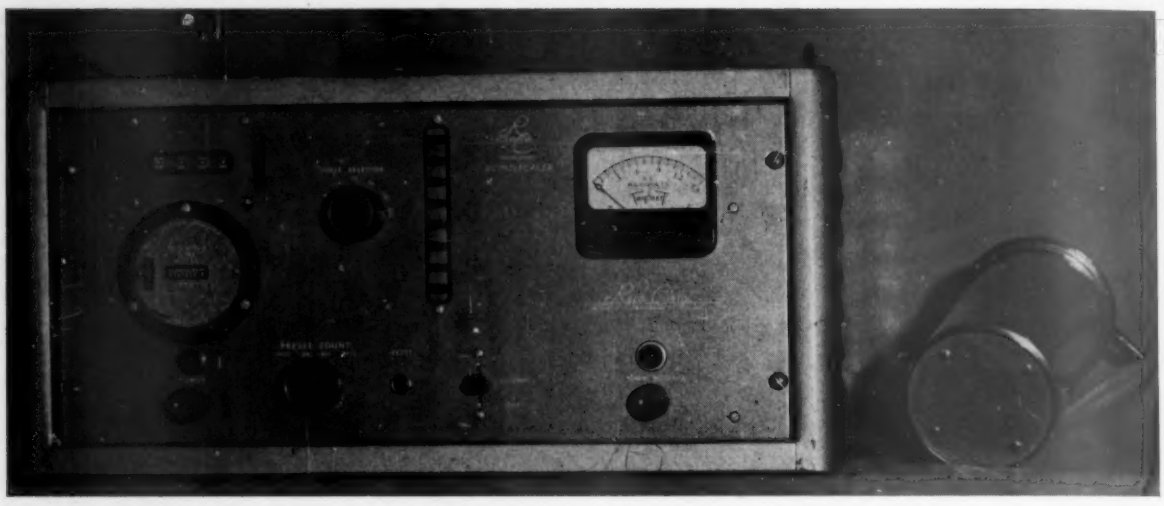

Fig. 3. Scintiscaler and scintillation detector used in localization of the placenta with isotopes. (Official photograph, U. S. Navy.)

cesarean section were utilized during this investigation.

Technique

The patients selected for study are given 10 μc* of radioiodinated human serum albumin in the antecubital vein. Care is taken so that neither the patient nor the operator is contaminated with radioactive material. A 10 minute period is allowed for the isotope to mix thoroughly with the blood. During this time the abdominal surface over the gravid uterus is divided into 12 approximately equal sections (Fig. 1). This is accomplished by measuring the height of the fundus above the symphysis and dividing this area into 4 equal horizontal parts. Each horizontal part is then divided into thirds, resulting in a total of 12 sections. A mark is placed in the center of each section, over which the counter is centered (Fig. 2). The xyphoid process is also marked and this is used as a reference point.

A scintillation detector with a sodium iodide crystal and wide-angle aperture is used to detect the gamma radiation emanation from the injected radioactive material (Fig. 3). Neither columnation nor lead filters are used. With the counting aperture placed flush with the skin surface, successive counts are taken over the xyphoid and over the center of each section. A scaler then records the time it takes to count the pre-set number of 2,560 radioactive impulses. From these data the background radiation is subtracted and the counts per second are obtained. These counts are then stated as a percentage of the reference point count (xyphoid count). The counts expressed in this way give rise to patterns which are easily interpreted and can be compared between patients.

Thirty drops of a saturated solution of potassium iodide in three divided doses over a 24 hour period is given to the patient to saturate the maternal and fetal thyroid glands, thus preventing the uptake of the radioactive iodide.

Results

Interpretation of the results obtained is not very difficult when the over-all pattern is viewed. Certain factors affect specific sections. Counts taken on nonpregnant women reveal that the liver gives rise to a higher count in the right upper section. The upper sections are also affected by the heart and

*The amount of radioiodinated human serum albumin has recently been reduced to 5 μc without any appreciable change noted in the accuracy of the method.

spleen. As a result, there is a slight decrease in counts as one proceeds from the upper to the lower abdomen. Also, the proximity of the iliac vessels to the lower lateral sections accounts for a slightly higher count in these as compared to that in the lower center sections.

Numerous formulas have been tried to determine which of the percentage counts are significant so that a more objective analysis can be made. The average of the highest count and the lowest count has proved to be of value in two ways. The percentage counts above this figure are usually grouped together over the placental site and constitute the significant counts. This average figure is also of some value in determining whether or not the placenta is on the anterior or posterior wall of the uterus. If this figure is above 70, the placenta is located on the anterior wall and, if below 70, on the posterior wall. The differentiation between these areas is due to the variation in distance between the placenta and the detector. Occasionally, all the counts appear to be at baseline levels in all the sections. In such instances the placenta is diagnosed by exclusion as being located on the posterior midline wall of the fundus.

With these criteria, the position of the placenta was described graphically and was stated to be in the fundus or lower segment and on the anterior or posterior wall. When the placenta was localized in the lower uterine segment, it could not accurately be determined if it was a low-lying, partial, or total placenta previa.

The actual placental site was determined subsequently by direct visualization at the time of cesarean section or by manual exploration of the uterus after vaginal delivery.

Two typical cases in this study of placenta previa are briefly summarized in Figs. 4 and 5.

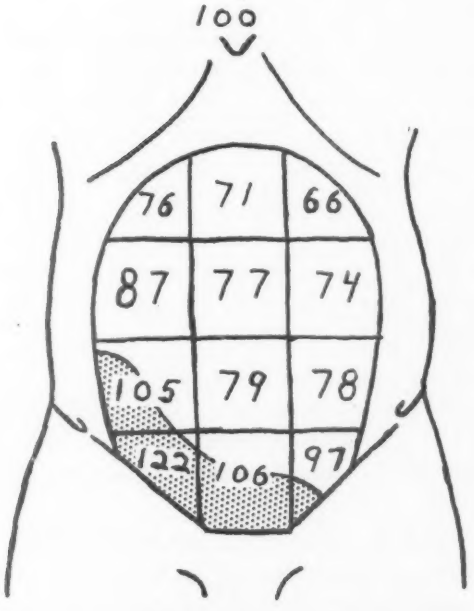

Fig. 4. Case 1. A. H., a 33-year-old gravida ii, para i, with third trimester bleeding. Isotope placental localization at 34 weeks' gestation. Average figure is 94; therefore, the significant counts are 105, 122, 106, and 97. Interpretation: placenta on the right lateral and anterior wall of the lower segment. Patient was delivered by cesarean section at 38 weeks' gestation. Findings: total placenta previa as depicted in the shaded area.

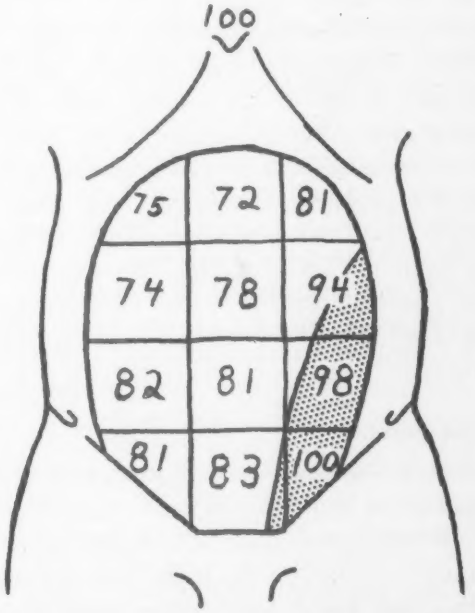

Fig. 5. Case 2. E. R., a 33-year-old gravida iii, para i, with third trimester bleeding. Isotope placental localization at 35 weeks' gestation. Average figure is 86; therefore, the significant counts are 94, 98, and 100. Interpretation: placenta on the left lateral and anterior wall of the lower segment. Patient was delivered by cesarean section at 37 weeks' gestation. Findings: partial placenta previa as shown in the shaded area.

Table I. Accuracy of prediction of placental implantation site

	Correct	*Equivocal*	*Incorrect*	*Total*
Repeat cesarean section				28
Placenta localized in fundus	27	0	0	
Placenta localized in lower segment	1	0	0	
Third trimester bleeding				23
Placenta localized in fundus	15	1	0	
Placenta localized in lower segment	7	0	0	
Total	50	1	0	51

Table I demonstrates the accuracy of our predictions. The placental site was accurately localized in each patient who was subsequently delivered by cesarean section. There were no incorrect predictions in which the patient was thought to have a placenta previa and did not or in which the placenta was predicted to be in the fundus and subsequently was found to be a placenta previa. The equivocal result occurred in a patient with third trimester bleeding who later was delivered vaginally. The placental site was thought to be in the fundus, but manual exploration after a normal labor and delivery revealed it to encroach upon the lower uterine segment. There were 8 cases in which the placenta was accurately predicted to be in the lower uterine segment. Of the 23 patients studied with third trimester bleeding, 7 had bleeding due to placenta previa.

Comment

For the method of radioisotope placental localization to be of practical value, it must be demonstrated that it is simple in technique, relatively safe from harmful radiation, and has a high degree of diagnostic accuracy. The radioactive substance, scintillation detector, and scaler are standard equipment for diagnostic studies in most isotope laboratories.

The scintillation detector is an instrument composed of a scintillator crystal and a photomultipler. It is used to detect the gamma radiation emanating from the radioactive substance. The scaler is an electronic counting device with a timer which is capable of registering a weak impulse at high speed. Lead filters and columnation did not improve the counting accuracy. There was not enough contrast between the placental site and the background areas to produce a graphic pattern with a scintillation scanner.

The radioiodinated serum albumin is a commercial product readily available and relatively inexpensive. It has a half life of 8 days and has to be renewed about every 2 to 4 weeks. The combined radioiodide protein molecule behaves biologically like the human serum albumin from which it is derived.[15] This material mixes completely with the circulating blood within 10 minutes. After one hour, appreciable amounts of the radioactive material start to mix with the extravascular fluid and also begin to undergo metabolic degradation. Therefore, the counts should be taken from 10 minutes to one hour after the radioactive substance is injected into the vein.

Five to 15 per cent of the administered radioactive iodide is excreted in the urine daily. There is very little placental transmission of the combined radioiodide and albumin because of the high molecular weight of the protein.[16] The free radioiodide which is present after the metabolic degradation of the combined material, however, crosses the placental barrier and can be taken up by the fetal thyroid gland.[17] To prevent the possibility of damage to the thyroid in this manner, the iodide uptake of the gland is blocked by the administration of a saturated solution of potassium iodide.

There is very little movement and no unnecessary manipulation of the patient. She is transported to the isotope laboratory by stretcher cart. The test is performed with the patient on the stretcher, and she is then transported back to the obstetrical unit. The entire procedure requires about 30 minutes; the results are immediately available and consultation with another physician is not required.

When the safety of this procedure is evaluated the primary concern is the amount of radiation to which the fetus is exposed. The amount of radiation associated with radiographic placentography is extremely variable with estimates running from 0.5 to 3 r.[8, 18-20] Using 5.0 μc of radioiodinated human serum albumin, Weinberg and associates[13] estimated that the fetus would receive a maximum of 20 milliroentgens. Under the same conditions Hutchinson and associates[14] calculated that the fetus would have a maximum exposure of 70 milliroentgens. With 10 μc of the radioactive material used, as in this study, the maximum fetal radiation to total decay was calculated to be approximately 50 milliroentgens. This was estimated by assuming that the fetus is constantly bathed in one tenth of the maternal blood volume, or about 600 c.c. This figure is in agreement with the estimated radiation hazard from radioiodinated human serum albumin used for other clinical purposes.[15, 21] Therefore, with this technique, there appears to be decidedly less radiation sustained by the fetus than with standard roentgen placentography methods.

Although the ultimate evaluation of the diagnostic reliability of this technique will depend upon more extensive clinical trials, our preliminary study of 51 cases indicates that there has been a high degree of diagnostic accuracy to date. Placental site localization by this method proved to be 100 per cent accurate in all cases of repeat cesarean section and in patients in whom the placenta was localized in the lower uterine segment. The one equivocal result occurred in a patient with third trimester bleeding who was delivered vaginally.

Further studies are in progress to reduce the amount of isotope used, to improve the technique, and to determine more objective means of interpretation.

Conclusions

1. Radioisotope localization of the placenta appears to be a simple and safe method for the detection of cases of placenta previa, and, from the results of our study to date, it is highly accurate.

2. The conservative management of cases of placenta previa can now be pursued on a more substantial footing, thereby eliminating the need for prolonged hospitalization in certain instances where the diagnosis is uncertain.

3. This method of placental localization carries the lowest radiation hazard to the mother and baby as compared with other methods of roentgen placentography.

We wish to express our appreciation to the personnel of the Isotope Laboratory, United States Naval Hospital, San Diego, for their assistance in carrying out this study.

Addendum. Since this article was submitted for publication, the placenta has been correctly localized by this isotope technique in 47 additional cases, including 4 patients with placenta previa. This brings the total number of cases studied to 98 with 12 patients having placenta previa. The placenta was correctly localized in the fundus or lower uterine segment in each instance.

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Use of femoral arteriography in assessment of bleeding in pregnancy

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THE problem of bleeding during pregnancy is one in which the etiology is often obscure. The use of percutaneous retrograde femoral arteriography has been studied at the United States Naval Hospital, St. Albans, New York, for the past 3 years.[1, 2] The value of this technique in bleeding in all stages of pregnancy was recognized. As a result, an intense survey of all cases of bleeding in pregnancy over a 6 month period was made. The details of this survey serve as the basis of this article.

Methods

A standard procedure has been evolved for those patients who present with the complaint of bleeding during pregnancy. In patients in the first trimester the usual methods of diagnosis, namely, history, laboratory studies, and speculum and bimanual examinations, are employed to establish obvious causes of bleeding. A similar procedure is followed in those patients who present early in the second trimester, while those in the last half of pregnancy are managed as follows:

History is obtained and physical examination, excluding pelvic and rectal portions, is carried out. Blood is drawn and sent to the laboratory for blood count, typing, and cross-matching of whole blood for possible transfusion. Intravenous infusion of glucose is started with an 18 gauge needle. A speculum examination is then carried out in the examining room to visualize the vagina and cervix and exclude local causes of bleeding. An attempt is made to perform this examination during the active phase of bleeding so as to observe the site of origin accurately. Attention is paid to the presence or absence of a mucus plug in the cervix. No digital examination is carried out. If no local cause of bleeding is found, a percutaneous retrograde femoral arteriogram is taken. If a central placenta previa is demonstrated, the patient is treated expectantly until 38 weeks of gestation when elective cesarean section is performed. Adequate blood replacement is maintained during this waiting period.

In those cases in which arteriography has not demonstrated a central placenta previa but in which the placenta is found to be marginal or low lying, a vaginal examination is performed at the appropriate time with a "double setup."

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The opinions expressed are those of the authors and do not necessarily reflect the views of the Navy Medical Department.

Table I

Patient	Weeks gestation at time of test	Significant clinical findings: Pretest	Significant clinical findings: Follow-up	Placentogram	Examination of placenta	Infant	Delivery after test (days)
B. F.	36	Painless vaginal bleeding; continued during labor	Delivery of premature infant	1. Normal implantation 2. No pooling	1. Adherent marginal clot	Living and well	Test performed intrapartum
A. C. W.	34	Repeated episodes of moderate bleeding associated with contractions	Intermittent bleeding with occasional contractions	1. Placenta enters true pelvis 2. Pooling	1. Low-lying posterior placenta 2. Organized infarct (cesarean section)	Living and well	35
B. N.	17	Repeated episodes of heavy bleeding associated with contractions	Placenta expelled prior to delivery of fetus	1. Central placenta previa	1. Entire surface covered by recent adherent clot	Immature stillborn	9
P. K.	40	Moderate painless bleeding	Continuation of bleeding	1. Placenta enters true pelvis	1. Placenta attached to lower portion of uterus	Living and well	3
M. S.	34	Painless bleeding	No recurrence of bleeding	1. Normal implantation	1. Manual removal of adherent placenta high in uterus	Living and well	42
P. D.	40	Moderate painless bleeding	Continuation until delivery	1. Normal implantation 2. No 15 second film	1. Recent adherent clot	Living and well	3
L. M.	23	Repeated moderate painless bleeding	Asymptomatic	1. Normal implantation	1. Normal	Living and well	100
V. B.	32	Repeated moderate painless bleeding	Asymptomatic	1. Normal implantation 2. Pooling	1. Two organized infarcts	Living and well	46
J. McD.	4	1. Repeated painless bleeding 2. Uterus 16 weeks size 3. Pelvic masses	Continuation of same	*	1. At operation uterus opened and placenta in fundus 2. Entire uterine cavity filled with hydatidiform mole 3. Bilateral lutein cysts in pelvis		3 (hysterotomy)

B. S.	25	Repeated massive painless bleeding	1. Continuation of same 2. Final episode with onset of labor	1. Central placenta previa (posterior)	Central placenta previa extending along posterior wall (at time of cesarean section)	Living and well	63
G. A.	37	1. Serosanguineous cervical discharge with uterine contractions	Continuation	1. Normal implantation 2. Pooling	1. Adherent clot	Stillborn; grossly malformed	8
E. J.	15	Repeated episodes of minimal painless bleeding; slightly enlarged soft uterus; 10 cm. right adnexal mass		Extrauterine placental sinusoids supplied by adnexal artery	Intraligamentous pregnancy on right side	15 cm. fetus in amniotic sac	Operation—day of test
R. P.	21	Repeated episodes of spotting throughout pregnancy	Continuation	1. Normal implantation 2. No pooling	Normal	Living and well	126
S. P.	40	Minimal painless bleeding	Asymptomatic	Normal implantation	Normal	Living and well	2
T. D.	23	Moderate bleeding with cramps	Continued; followed by onset of labor	1. Normal implantation 2. Pooling of dye	Adherent marginal clot; complete circumvallate placenta	Immature; neonatal death	6
J. H.	20	One month of moderate bleeding associated with cramps	No further bleeding and gradual cessation of cramps	Left cornual implantation			Not delivered at time of report
A. S.	30	Ruptured membranes; slight painless bleeding	Continuation until delivery	1. Normal implantation	Normal	Premature neonatal death	14
G. McG.	37	Severe bleeding with cramps	Continuation until delivery	1. Normal implantation 2. No pooling	Adherent marginal clot extending onto membranes	Living and well	1
C. B.	37	Ruptured membranes; severe bleeding associated with uterine contractions; uterus tender on right	Continuation until delivery	1. Normal implantation 2. No pooling	Adherent marginal clot	Living and well	1
L. H.	20	Massive bleeding with cramps	Intermittent heavy vaginal bleeding	1. Low lying placenta 2. Pooling	Adherent clot covering ⅓ of placenta	Premature stillborn	45
R. B.	31	Minimal painless bleeding	Asymptomatic	1. Normal implantation 2. Pooling	Normal	Living and well	63

*Placental sinusoids were seen in the upper half of the uterus. Numerous fine vessels were seen within the true pelvis radiating medially from the large vessels.

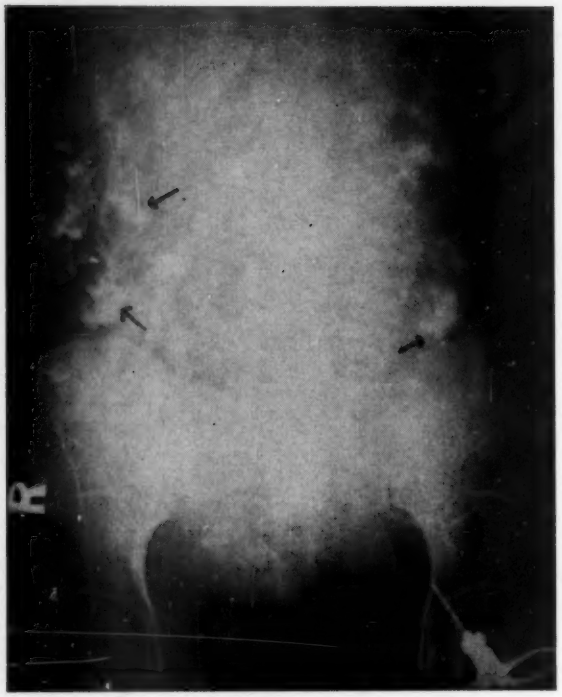

Fig. 1. Case 18. Arteriogram in a term pregnancy. Arrows indicate contrast material in the placental sinusoids. This was a normally implanted placenta. Film shown was taken 3 seconds after injection of dye.

Technique

The patient is prepared by an intramuscular injection of 100 mg. of Demerol with 25 mg. of Sparine if no contraindication exists. The patient is placed in the supine position and a tourniquet is placed high on the thigh on the side of injection. The inguinal area is cleansed with 70 per cent alcohol, and sterile drapes are placed about the site of injection. The femoral artery is palpated and 2 per cent Cyclaine is injected into the tissues adjacent to the artery immediately superior to the inguinal ligament. A small incision is made over the artery to prevent binding with insertion of the needle. A 16 gauge Lindeman needle is inserted cephalad into the artery. A saline-filled disposable plastic tube with a three-way stopcock attached to a 30 c.c. syringe is then connected to the needle. A 1 c.c. test dose of 50 per cent Hypaque is injected and 5 minutes allowed to elapse. Immediately prior to performance of the arteriogram the pressure cuff is inflated well above systolic pressure and 30 c.c. of the contrast material are injected as rapidly as possible (approximately within 2 seconds). The tourniquet is released immediately upon conclusion of the injection. Roentgenograms are obtained 3 and 15 seconds after completion of the injection. If the placenta is seen to be low lying on the anteroposterior projection, a second injection is made and a lateral film obtained at 3 seconds. The lateral projection gives more precise localization of the placenta.

Upon completion of the study the needle is removed and pressure applied at the injection site by the operator for 10 minutes.

Comment

Table I sets off the clinical and arteriographic findings in the 21 patients studied in this series. The salient features of this table are:

1. Determination of presence of placenta. In all the cases of this series, regardless of gestational age, it was possible to demonstrate placenta arteriographically (Fig. 1). Fernstrom[3] reported visualization of placental sinusoids in intrauterine pregnancy as early as 8 weeks. Our experience has substantiated this finding. However, to our knowledge, no cases of intrauterine pregnancy have been studied prior to this period. Fernstrom reports visualization of placenta at 5 weeks in an ectopic pregnancy. In Case 12, an abdominal pregnancy of 15 weeks' duration, the placental sinusoids were well visualized. It is interesting to note that in this case the placenta received its blood supply from the greatly hypertrophied adnexal branch of the uterine artery rather than directly from the uterine artery itself (Figs. 2*A* and 2*B*). In intrauterine pregnancy it is the ascending portion of the uterine artery which supplies the placenta. In Case 9, a hydatidiform mole, placental sinusoids were visualized at 4 weeks' gestation (Figs. 3*A* and 3*B*). This, however, is a case of abnormal trophoblastic proliferation and accounts for discrepancy in gestational

Fig. 2*A*. Case 12. Arteriogram in an abdominal pregnancy of 15 weeks. Film shown was taken immediately upon completion of injection. *U*, Hypertrophied right uterine artery. *A*, Adnexal branch supplying the placenta in this case.

Fig. 2*B*. Case 12. Film taken 3 seconds after that in Fig. 2*A*. This shows the placental phase of the arteriogram, and the arrows indicate the placental sinusoids.

age and visualization of placenta arteriographically.

2. Localization of the placenta. The accurate position and extent of the placenta can be determined by arteriography at all stages of pregnancy and regardless of fetal presentation. We use the anteroposterior roentgen projection to determine whether any portion of the placenta lies within the true pelvis. The lateral projection is used only to determine the exact localization of the placenta found within the true pelvis.

In Cases 3 and 10 total placental previa was diagnosed at 17 and 25 weeks of pregnancy, respectively. The first case illustrates the value of arteriography in accurately defining the cause of bleeding in early pregnancy. This patient went on to delivery one week later in spite of complete bed rest and repeated blood transfusions. At the time of delivery the arteriographic diagnosis was confirmed. In the second case (Fig. 4) the pregnancy was slightly more advanced and with the same method of treatment a successful termination of the pregnancy was accomplished. Arteriography will enable the obstetrician to circumvent the previous policy of watchful waiting before an accurate diagnosis of placenta previa can be made.

3. Determination of presence of abruptio placentae. Prior to this study the diagnosis of abruptio placentae could only be inferred by clinical signs. During the course of this study a previous isolated observation was confirmed, namely, pooling of contrast material in extravascular spaces. By pooling is meant a discrete oval accumulation of dye which is characteristically observed on the film taken 15 seconds after injection. This finding is to be distinguished from the irregular, patchy accumulations of dye seen 3 seconds after injection which are characteristic of placental sinusoids. Cases 2, 8, 11, 15, 20, and 21 demonstrated this roent-

Fig. 3*A*. Case 9. Arterial phase of an arteriogram in the case of a hydatidiform mole. Arrows indicate uterine artery.

genologic feature (Fig. 5). Examination of the placenta at the time of delivery established correlation of this radiologic finding with the histology of the placenta. In Cases 2 and 8 sufficient time elapsed to allow organization of the infarcted area. In the other cases the interval between examination and delivery was shorter and the placentas exhibited recent adherent clots. In Case 15 which clinically exhibited the findings of "marginal sinus rupture" the radiologic findings could not be distinguished from those of premature separation of the placenta.

In Cases 1, 18, and 19 in which the gross appearance of the placenta revealed an adherent marginal clot which could be interpreted as evidence of "marginal sinus rupture" or abruptio placentae, the radiologic findings did not show pooling of dye. There was observed, however, persistence of dye within the placental sinusoids on the 15 second film. Further investigation may indicate that this is evidence of impeded placental circulation.

It is important to note that the technique as outlined above requires no special equipment except for the Lindeman needle. A 120 kv., diagnostic x-ray machine was used. In cases such as the abdominal pregnancy, however, much more information can be gained if a serial x-ray changer is available. This permits exposures to be made at half second intervals during the critical period from 2 seconds to 4 seconds following injection of the dye. By this means the arterial, placental, and early venous phases can be visualized.

There were no complications either major or minor in the 21 cases included here. In our total experience extending over 3 years and numbering 250 cases not one serious complication has occurred. In 2 cases extravasation of the dye occurred but no additional analgesia or local anesthesia was required. In 2 cases small local hematomas formed following the procedure but resolved

Fig. 3*B*. Case 9. Placental phase (film taken 3 seconds after that in Fig. 3*A*). Placenta here could not be distinguished from normal placenta and grossly normal placental tissue was present at time of hysterotomy. Arrows indicate placental sinusoids.

quickly and uneventfully. The possibility of sensitivity to the contrast material is always present. To date this has not been encountered.

At the United States Naval Hospital, St. Albans, New York, the routine use of percutaneous retrograde femoral arteriography in diagnosis of placenta previa continues. In addition, the use of this technique as a research tool continues in an effort to add to the existing knowledge of placental circulation both normal and pathologic. We do not advocate routine use of this technique; however, we do hope others will take it up in an effort to confirm our findings as well as to clarify some of the questions raised here.

Fig. 4. Case 10. Placental phase in a patient at 25 weeks' gestation. Arrows indicate placental sinusoids filling pelvis. The diagnosis of central placenta previa was confirmed at cesarean section at 34 weeks.

Fig. 5. Arteriogram in case of abruptio placentae. Film shown was taken 15 seconds after injection of contrast material. Normally all of the dye has disappeared by 7 to 8 seconds after injection. This pooling of contrast material was seen in 6 cases in this study, and in each case the diagnosis of abruptio placentae was confirmed at delivery.

Summary

1. An arteriographic study was made of 21 consecutive pregnant patients (over a 6 month period) who presented with unexplained vaginal bleeding.

2. It has been possible by this method to determine the existence and site of the placenta and presence of abruptio placentae.

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Placental localization with use of radioactive iodinated human serum albumin

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PAUL E. KRATZ, M.D.

Cape Girardeau, Missouri

WHEN there is bleeding in the last trimester of pregnancy, a problem in differential diagnosis always arises. Placenta previa and premature separation of the placenta are the primary causes to be differentiated. Since the treatment of these two conditions is frequently different, it becomes important for the obstetrician to determine as precisely as possible the position of the placenta; at least it is helpful to know if the placenta is implanted above the cervical os. Vaginal examination may be dangerous and may precipitate massive bleeding. The vaginal examination may also be limited because of inadequate cervical dilatation. The other method of diagnosis available to the obstetrician is x-ray examination including soft tissue studies, contrast studies, and/or displacement techniques. X-ray studies have been found to be 85 to 90 per cent correct, but this method of diagnosis necessitates manipulation and transportation of an already seriously ill patient. Excessive manipulation of these patients, particularly when bleeding may have finally been controlled, may be extremely dangerous. These various x-ray examinations are also time consuming and are usually requested on an emergency basis at times when the x-ray department may not be completely staffed. However, these procedures should be done if the patient's condition will allow.

A method for immediate bedside localization of the placenta by use of radioactive isotope would be of great aid to the obstetrician. The purpose of this paper is to present a preliminary report on such a method of determining the position of the placenta. The general technique was first described by Weinberg and associates[3] in 1956, who used radioactive sodium. Their study was conducted on a group of 20 cases and the results were encouraging. A correct diagnosis of placental localization was accomplished in 14 of the cases, was incorrect in none, and was doubtful or questionable in 6. The main difficulty encountered in this study was due to the fact that the half life of sodium was only 16 hours. The time factor limited the accuracy, and the diffusibility of the sodium with loss into the tissues may have been a factor in the questionable cases. To eliminate these difficulties Weinberg and co-workers[2] reported in 1957 the use of radioactive iodinated human serum albumin which has a half life of 8 days. This material consists of a larger molecule and therefore does not diffuse out of the vascular system. The radioactive iodine having a half life of 8 days lends greater accuracy to the procedure by allowing the readings to be taken at leisure and to be completely reproducible for several hours after the injection because the material remains confined to the vascular space for 16 hours. Radioactive iodine is also a

This work authorized by the Atomic Energy Commission under License No. 24-128-2 and No. 24-128-3 at Southeast Missouri Hospital and under License No. 24-158-2 and 24-158-3 at St. Francis Hospital.

more readily available isotope in the average hospital.

Some consideration in regard to the radiation dosage to the fetus is necessary before the procedure can be used routinely. When radioactive iodine having a half life of 8 days is used, the total dosage to the fetus is estimated at 0.02 r or one fifth of the radiation dosage when sodium is used. The iodine in the large albumin molecule is liberated in the human body at a rate of 5 per cent per day which indicates that one twentieth of the injected dose of 5 μc, or 0.25 μc, is available each day for thyroid uptake. Calculation along these lines by Weinberg[2] indicated that the total maximum radioactivity available to the fetal thyroid is 3.0 r in the average patient. This is thought to be below the radiation that the thyroid receives in x-ray pelvimetry. Another index as to the safety of the usage of radioactive iodine is that the dosage used is one third to one eighth of that used in diagnostic uptake studies of the thyroid. The Atomic Energy Commission considers 140 μc a safe maximum tracer dose for patients in this weight group. Weinberg[2] also reports that a 24 hour follow-up of infants delivered from mothers injected with radioactive isotope fails to show any detectable radioactivity with a scan of the thyroid area. We have, however, not attempted to scan the thyroids in the infants in our series.

Technique

The basis for the study and the use of radioactive iodinated human serum albumin is that the placenta represents a pool of blood where the isotope accumulates in quantities comparable to that in the heart as long as the isotope remains in the circulation. The material is injected intravenously and allowed to mix with the blood in the entire cardiovascular system, and counts are obtained over the various portions of the uterus as well as over the heart with use of a collimator attachment on a scintillation counter. The general technique is similar to that reported by Weinberg and his associates.[3] A few changes have been made which we feel may add to the accuracy of the examination. Authorization for this study was obtained from the Atomic Energy Commission on approval of a series of 25 cases to evaluate the method.

The volunteers were informed of the intent of the study and the value of the examination, and written consent was necessary and was required before the injection of the isotope.

The usual precautionary techniques were used to avoid overexposure of the patient and personnel. Only one examination on each of the volunteers was done with no more than one isotopic administration per patient. During the early stages of our series as little as 2½ to 3 μc was injected, but we found that with this small quantity of radioactive material the differential in the counts over the uterus and the heart was so small that some difficulty was encountered in localizing the placenta. It is felt that 5 μc is more desirable and more accurate in this localization. Also during the early stages of our series only 30 seconds was allowed for the admixture of the radioactive material in the blood. We found with experience, however, that the results were more accurate and reproducible after an interval of 5 to 10 minutes following the intravenous injection. Counts were obtained over 12 areas outlined on the uterus as shown in Fig. 1. Counts were also obtained in the right and left flanks with the collimator almost perpendicular to the spine in both of these areas. These two areas for counting were thought to be of value in the localization of the placenta posteriorly.

Patients were scheduled for study in the last trimester of pregnancy. In our series the following groups of patients were examined: (1) patients who were scheduled to undergo an elective cesarean section; (2) patients with bleeding in the last trimester; (3) multiparous patients in whom the placental site could be determined by manual removal at the time of delivery; and (4) patients with suspected intrauterine fetal death. This last group was added since it was felt that this type of examination would

PLACENTA LOCALIZATION DATA

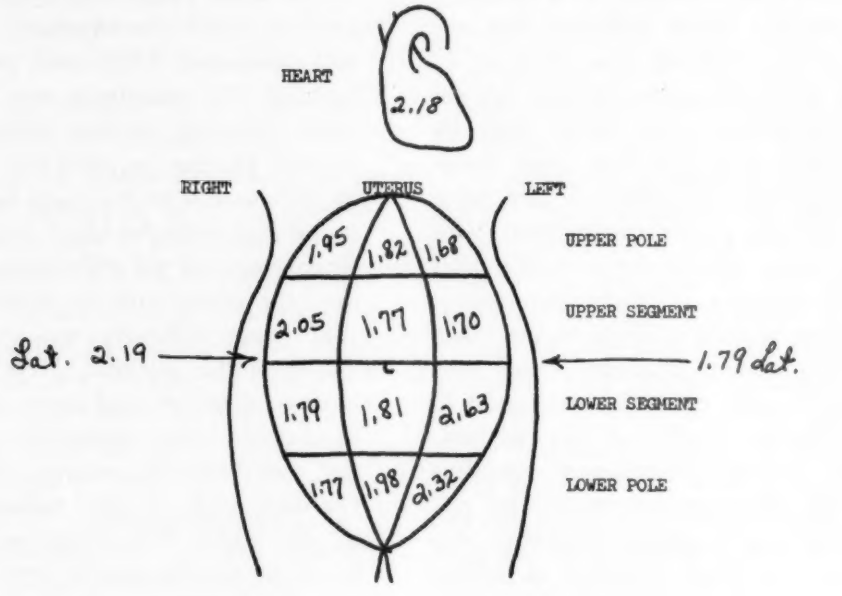
NAME Mrs. L. M. AGE 30 PARITY ii

E.D.C. 8/20/58 DATE of TEST 7/24/58 SOURCE NO. Lot 84 263

DATE of DELIVERY August 12, 1958 CALIB. DATE 7/7/58

METHOD ROOM NO.

REMARKS Uncomplicated pregnancy, 38 weeks gestation.



NUCLEAR CONSULTANTS INC.
St. Louis, Mo.

PHYSICIAN E. Johnson M.D.

Fig. 1. Sample localization chart indicating counts in the areas indicated and in flanks. This is the chart of the one case in which there was error and the low counts are shown which we feel accounted for the error.

also be of value in the determination of fetal death.

In cases where bleeding occurred in the last trimester the other usual diagnostic measures, such as x-ray examination and/or vaginal examination were carried out as indicated.

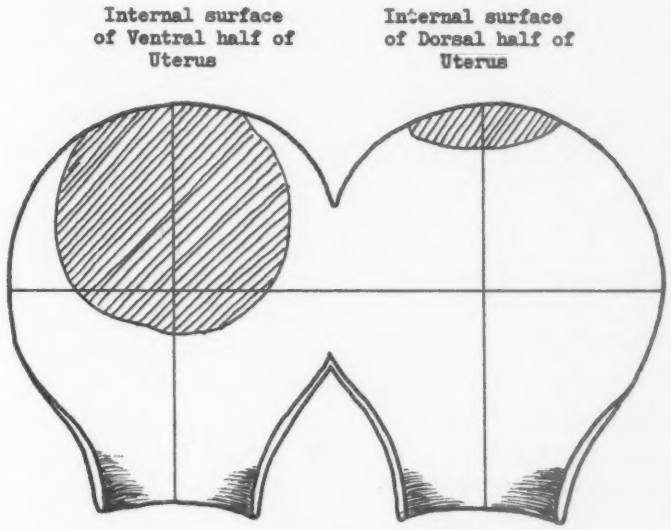
A blind study was done with the radiologist performing the test and recording the counts over the uterus and in the right and left flanks as described. A written report was completed indicating the placental site as determined with the study of radioactivity. This material was filed until after delivery with a notation to the obstetrician that the determination of the placental site should be determined for correlation with the predelivery examination. The obstetrician at the time of delivery then localized the placenta either visually at cesarean section or by manual palpation immediately after delivery. This is charted on a form as indicated in Fig. 2. The localization at delivery was recorded and, after completion of the 20 cases here reported, the findings by the radiologist and the obstetrician were compared. Actually, 25 cases were studied but 5 were excluded because of technical

NAME Mrs. L. M. HOSPITAL St. Francis
HOSPITAL # 58-3244
DR. Kratz Date of Delivery 8/12/58

Complications:

Method of Delivery - Section ☐ Vaginal ☒

Unable to determine placental position ☐



UTERUS IS SHOWN SECTIONED IN FRONTAL (OR CORONAL) PLANE THUS REVEALING INTERNAL SURFACES OF DORSAL AND VENTRAL HALVES.

▨ Area of placental site

PHYSICIAN Paul R. Kratz M.D.

Fig. 2. The form completed by the obstetrician indicating the placental site at delivery. This is the findings on the case localized in Fig. 1 and indicates the error.

difficulties or an inability to establish clinically the location of the placenta.

Results

Table I shows the results in 20 cases in which localization was done by the radiologist with this technique and then compared with the actual findings at cesarean section or after manual removal.

After reviewing the findings as shown in Table I, we feel that some explanation for the large number of incorrect localizations in regard to lateral and anterior or posterior position is necessary.

One possible explanation is the rotation of the uterus that occurs with pregnancy. As the uterus grows out of the pelvic cavity it usually rotates slightly to the right so that its left margin is directed more anteriorly than the right. Occasionally the torsion may

Table I

Case No.	Horizontal localization		Vertical localization	
	Incorrect	Correct	Incorrect	Correct
1	x			x
2	Slightly			x
3		x		x
4	Slightly			x
5		x		x
6		x		x
7	Slightly			x
8		x		x
9		x		x
10	x			x
11	x			x
12		x		x
13		x		x
14	x			x
15	Slightly			x
16	Slightly		x	
17	Slightly			x
18	Slightly			x
19		x		x
20		x		x
Total	11*	9	1	19

*Four totally incorrect; 7 slightly incorrect.

be in the opposite direction. Therefore, localization after the uterus has contracted may be as much as 90 degrees or more to the right or left of the localization with the radioactive iodine study.

Actually, the vertical localization in the series that we have completed was correct in 19 of 20 instances, and the fact that the amount of radioactive material injected was so small may have accounted for the erroneous result in this one case. We felt that a significant factor in the accuracy of this study was the activity of the isotope administered for the examination. As indicated previously, in a number of instances in which the source was a week to 2 weeks old and contained less than 3 μc of activity, localization was more difficult and probably not as accurate. It is felt that a source of at least 5 μc is necessary.

Another significant finding was that the iodinated human serum albumin is much more stable and counts obtained after an interval of 10 minutes are more reproducible and accurate. This allows for better admixture of the material in the circulation and also for adequate pooling in the uterus.

In the small series that we have completed we feel that the additional readings obtained in the right and left flank areas gave us better insight to an anterior, posterior, or lateral lying placenta. We feel that these additional counting areas should add to the accuracy of the procedure as a larger number are performed.

Conclusions

This is a preliminary report which is not statistically valid because of the small number of cases. However, a trend is indicated in our findings. A method of determining the placental site is described. We feel this method has been shown by our results to be sufficiently accurate, safe, and easy to justify as an addition to the armamentarium of the obstetrician. The test, we feel, should complement but not replace existing methods of placental localization including x-ray examination. The one error in vertical localization has been partially explained and probably could have been avoided by the use of sufficiently active radioactive material.

Lateral localization was less than 50 per cent accurate but does not lessen the value of the procedure in determining placenta previa.

This study is still in progress and a subsequent report will be made when the series reaches statistical validity.

Acknowledgment is given to the isotope laboratories at Southeast Missouri Hospital and St. Francis Hospital, which have cooperated with us in carrying out this work, and to Nuclear Consultants Corp. of St. Louis, for technical assistance and for providing the material and sources for this work.

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Continuous lumbar peridural anesthesia in obstetrics

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MANY methods of conduction anesthesia have been used in obstetrics since the introduction of spinal anesthesia in man by Bier in 1899.[1] It was not, however, until Cleland in 1933 demonstrated the sensory innervation of the uterus that such methods were based on neuroanatomical principle.[2] Since that time, conduction anesthesia has been valuable in obstetrics but none of the techniques advocated has proved entirely satisfactory. Each has had disadvantages as well as advantages. The present paper is concerned with the principles, techniques, and clinical application of one type of conduction anesthesia for obstetrics: continuous lumbar peridural anesthesia. ("Peridural," "epidural," and "extradural" are synonymous terms for the same anatomical space.)

The spinal peridural space is bounded superiorly by the foramen magnum where the spinal and periosteal layers of the dura fuse; inferiorly, by the sacral hiatus; anteriorly, by the posterior longitudinal ligament of the vertebral bodies; laterally, by the pedicles and intervertebral foramina; and, posteriorly, by the laminae and ligamentum flavum. Within this space lie the dural sac and its contents, spinal nerves as they cross the space to exit via the intervertebral foramina, sympathetics, arteries, veins, and connective tissue. A needle may be introduced into the peridural space at any vertebral level. The commonest approaches are via the sacral hiatus (e.g., caudal anesthesia) and via the interspinous spaces in the lumbar vertebrae. Local anesthetics placed in the peridural space may act at one of three sites: (1) by diffusing through the dura into the subarachnoid space, they may produce subarachnoid anesthesia; (2) they may act directly on nerve roots as they pass through the peridural space; or (3) they may act paravertebrally, following their extravasation through the intervertebral foramina. It is generally considered that the last is the method of action, but the simultaneous production of subarachnoid anesthesia cannot be entirely discounted.[3-5]

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Methods of identifying the peridural space

Successful peridural anesthesia depends upon accurate placement of the needle, through which the anesthesia is to be injected, into the peridural space. Many techniques have been devised to identify entrance of the point of the needle into this space, but most are dependent upon the demonstration of one of two phenomena: (1) either that negative pressure exists (or can be made to exist[3]) following insertion of a needle into the peridural space; this negative pressure technique has been identified with the "hanging drop" method[6] and

mechanical modifications of it[7, 9, 10]; or, (2) sudden disappearance of resistance to pressure applied to the needle by an attached syringe when the point enters the peridural space, and its modifications.[8, 11, 12]

In this clinic we have favored the loss-of-resistance technique to identify the peridural space by means of intermittent advancement of the needle and pressure applied to the plunger of a syringe which has been attached to the needle once the latter has entered the ligaments.

Techniques of peridural puncture

The patient is placed in the lateral recumbent position with neck flexed on the chest and the thighs flexed comfortably on the abdomen. Oxygen and vasopressors must be at hand. The skin of the back is cleansed with antiseptic solution and draped in sterile fashion. The lumbar spinous processes are identified by palpation and a midline skin wheal raise over the appropriate lumbar interspace, usually the third. A 17 gauge styletted Tuohy needle is inserted into the interspinous ligament through the skin wheal. When the needle is firmly within the ligament, the stylet is removed and a 2 ml. syringe filled with anesthetic solution (water,[13] saline,[14] or air[15] may also be used) is attached to the needle. Intermittent pressure is then applied to the plunger of the syringe. When the bevel of the needle is within the ligaments, a distinct bounce may be felt on the plunger. The needle and syringe are carefully advanced 2 to 3 mm. and resistance again tested. This is repeated until there is a sudden release of tension and the drug injects easily. Removal of the syringe should result in little or no backflow of drug through the needle. The triangular shape of the spinal canal in the lumbar region results in the widest peridural space at the midline posteriorly, the average distance between the ligamentum flavum and the dura being 5 mm. at this point[3]; therefore, the needle may be carefully advanced 1 to 2 mm. further into the space to facilitate passage of a fine plastic catheter about 4 cm. in a cephalad direction.

Paresthesias in the legs may occur on passage of the catheter. In this series it occurred 37 times (17.4 per cent). Flowers and associates[15] reported a 60 per cent incidence of a paresthesias. It is necessary to emphasize that the catheter must *never* be pulled back through the Tuohy needle once it has passed into the peridural space. Doing this may result in cutting the catheter in the peridural space. Bonica and co-workers[16] reported 3 cases in which this happened, and Frumin and Schwartz[17] cited several instances in which it was necessary to trephine the sacrum for this complication. Passage of the catheter more than 4 cm. allows the possibility of tying a true knot within the patient's peridural space. We are aware of one such instance.[18]

The needle is then withdrawn over the catheter, and the latter is taped in place and the patient turned supine. Negative pressure should be applied to the catheter with a dry syringe prior to slow injection of a 1 to 2 ml. test dose of anesthetic agent. It is essential that the test dose of anesthetic agent be delivered *through the catheter* and not through the needle as it is possible to puncture the dura with the catheter (two known instances in this series). Subarachnoid injection of the test dose is promptly manifested by the rapid appearance of spinal anesthesia. However, small test doses of 1 to 2 ml. result in low levels of spinal anesthesia and fewer and less profound physiological alterations. After the passage of several minutes without development of signs of spinal anesthesia, a definitive dose of drug is slowly injected through the catheter. When the anesthesiologist has become thoroughly familiar with the technique of peridural anesthesia, the time consumed in performance of this technique is equal to that of ordinary spinal anesthesia.

In this series, patients undergoing cesarean sections have received 2 per cent lidocaine with or without 1:100,000 epinephrine. Initial doses varied between 200 and 300 mg. Supplemental doses of 100 to 150 mg. were added every 30 to 35 minutes. Vaginal delivery dosage schedules varied with the in-

dividual anesthesiologists. The initial dose was usually 96 to 120 mg. of 1.2 per cent or 0.8 per cent lidocaine, with or without epinephrine. If the sacral segments were not anesthetized when delivery became imminent, the patient was placed in semi-Fowler's position and 1.2 or 2.0 per cent lidocaine added very slowly, and the drug allowed to gravitate downward within the peridural space and anesthetize the sacral roots. The duration of anesthesia usually was 90 to 150 minutes after the last injection of drug. Total dosage of anesthetic agent in the series averaged 300 to 500 mg. of lidocaine.

Plastic catheters, which are used once and discarded, are more desirable than 3.5 French ureteral catheters. The latter are more expensive and are damaged by autoclaving.

Results. The obstetrical procedures are summarized in Table I. The figures for low forceps reflect the delivery of most primiparas with outlet forceps. The fairly high percentage of midforceps operations is consistent with the practice in this clinic of administering conduction anesthesia to patients whose obstetrical situation is already complicated.

The indications for cesarean section are summarized in Table II. It is customary practice in this clinic to anesthetize all patients undergoing repeat cesarean sections, and as many as possible of those undergoing primary operations, with conduction anesthesia. Those undergoing repeat procedures rarely need to have general anesthesia when the anesthesiologist visits the patient on the night prior to operation. The mothers were invariably cooperative when the reasons for conduction anesthesia were explained and their fears allayed. Cesarean sections in this series were premedicated with 50 mg. of meperidine and 0.4 mg. of scopolamine. There was no depression of the infants by the Apgar method of scoring.[19] The 10 per cent of patients who earnestly desire unconsciousness after the birth of the baby were put to sleep with many combinations of supplemental medication as shown in Table III. It was customary in this series to give the mother some form of sedation routinely after the baby was removed to the nursery, usually an intravenous barbiturate or meperidine.

Table I

Spontaneous delivery		7
Low forceps delivery		56
Midforceps delivery		26
Scanzoni rotation	6	
Kjelland rotation	4	
Barton rotation	1	
Breech delivery		1
Cesarean section		126
Primary	39	
Secondary	49	
Tertiary	31	
Quaternary	7	

Table II. Indication for cesarean section

Repeat	87
Primary	
Cephalopelvic disproportion	13
Fetal distress	5
Placenta previa	2
Abruptio placentae, partial	1
Bandl's ring	1
Elderly primiparas with borderline pelvis	4
Bad obstetrical history; high-premium baby	2
Obstructing or multiple myoma	2
Transverse lie	1
Previous uterine operation (Lash; Manchester; Straussman; multiple myomectomy, 3; suture of cervix for incompetence)	7
Previously ruptured aneurysm of circle of Willis	1

Complications of peridural anesthesia in 212 cases

The complications are summarized in Table IV.

1. There were no complications at all in 131 cases, or 61.7 per cent of the entire series.

2. Systolic hypotension was the most common complication occurring in 50 cases (23.5 per cent). Hypotension is reflected in the fetus by bradycardia.[20] Maternal hypotension was promptly treated with intravenous and/or intramuscular vasopressors and usually responded immediately. Ephedrine or methoxamine were the drugs of choice. In 6

Table III. Supplemental medication (frequently in combination)

Seconal	27
Demerol	30
Nembutal	17
Pentothal	16
Morphine	16
Nitrous oxide	35
Cyclopropane	20
Required general anesthesia	7
General anesthesia at own request	13

cases, the hypotension occurred late in the procedure and was attributable to blood loss. Vasopressors were given prophylactically in 16 cases, mostly in cases of cesarean sections. Moore[21] reported that 60 per cent of patients undergoing cesarean section became hypotensive 15 to 20 minutes after the onset of peridural anesthesia. Bonica and associates[16] stated that 50 per cent of his patients had some degree of hypotension. Many of Bonica's cases however, were for upper abdominal, thoracic, or cervical procedures, as were the 71 per cent of cases cited by Frumin and Schwartz[17] in which there was hypotension of greater than 25 per cent of normal. Flowers and co-workers[15] recorded the use of vasopressors in about 21.5 per cent of patients undergoing cesarean section. In this series positioning of the legs somewhat higher than the trunk by flexion of the table and slight Trendelenburg provides sufficiently improved venous return to minimize hypotension.

3. Hypertension occurred only once and was attributed to the presence of epinephrine in the lidocaine. Since it was not excessive (128 per cent of normal) and provoked no symptoms in the patient, it was allowed to subside spontaneously over the next 30 minutes. Lidocaine without epinephrine was used for subsequent doses.

Table IV. Anesthetic complications

None		131
Hypotension		50
Hypertension		1
Accidental subarachnoid puncture		7
Postpuncture headache	3	
Total spinal anesthesia	0	
Generalized convulsion		2
Failure of anesthesia		5
Massive peridural block		0
Perinatal death		6
Congenital anomaly		4

4. Subarachnoid puncture occurred in 7 cases (3.3 per cent), mostly among the early cases in the series. Spinal anesthesia was successfully induced in 4 of these, but 3 of these 4 patients subsequently suffered post–lumbar puncture headache. In the 3 other cases, the peridural space was retapped at another level and a successful block achieved without subsequent spinal anesthesia or headache. In 2 of the 4 cases of spinal anesthesia, the plastic catheter apparently punctured the dura. In both, the needle was uneventfully placed in the peridural space and no spinal fluid appeared from the needle, but, after easy passage of the catheter, cerebrospinal fluid was aspirated. Both cases were continued as spinal anesthesia. In the other 2 patients, the dura was punctured by the needle and spinal anesthesia instituted at the appearance of spinal fluid. One of these patients was an achondroplastic dwarf undergoing cesarean section. Some reports urge that, when the dura is accidentally punctured, spinal anesthesia be used. However, Moore and his associates[22] were unable to demonstrate passage of radiopaque material into the subarachnoid space of fresh corpses after multiple punctures of the dura, and they cited 100 cases of peridural block after puncture without untoward results. Bonica and co-workers instituted peridural block in 44 of 79 patients in which the dura had been accidentally punctured.

There were no total spinal blocks in this series.

5. Generalized convulsions occurred twice. In one patient they were associated with severe pre-eclamptic toxemia, occurred in the immediate postoperative period, and were assumed to be related to the pre-eclampsia. This patient had had a lobotomy for psychiatric reasons in the past. In the other patient, convulsions occurred after general anesthesia had been induced although the peridural anesthesia was adequate. The sei-

zure occurred 30 minutes after induction with thiopental and cyclopropane and was stopped with thiopental. This is assumed to be a drug reaction, as careful questioning of the patient postoperatively failed to reveal any history of seizures. She had no signs of toxemia of pregnancy and there was no epinephrine in the lidocaine.

The convulsion rate as reported by Lund and associates[23] with lidocaine is 0.27 per cent (5 in 1870). Blundell and co-workers[24] mentioned 10 severe convulsive reactions, all of which occurred almost immediately after injection of the drug. Ansbro and collaborators[25] mention 2 seizures in 125 cases.

6. There were no massive peridural blocks in this series. There were no cases of moderate or marked asymmetry of blocked segments.

7. There were 5 cases of failure of anesthesia (2.3 per cent). In 2 cases the reason for failure was not obvious. In the other 3, one was subsequently found to be due to the fact that the catheter had been withdrawn when the needle was removed from the peridural space. In another, the anesthetic solution could be injected only with extreme difficulty and the possibility of passage of the catheter into or through the intervertebral foramen is to be considered. In the third case, the shape of the catheter after it was removed appeared to indicate passage through the peridural space and out through the intervertebral foramen. This patient was reblocked with successful anesthesia. Bromage[3] exhibits a radiograph which strikingly demonstrates this complication.

8. Neonatal death occurred 6 times. Four of the 6 deaths were due to respiratory insufficiency associated with prematurity, atelectasis, and hyaline membrane disease. The fifth death was of a previable premature infant, whose mother underwent cesarean section for intractably bleeding placenta previa. The sixth infant had widespread congenital abnormalities of the central nervous system including meningomyelocele, platybasia, hydrocephalus, and Arnold-Chiari malformation. There were no intrapartum deaths, and none of the perinatal deaths in this series appears attributable to the anesthesia.

9. Congenital anomalies occurred 4 times in this series. Two babies had bilateral clubfoot deformity; one had hypospadius; one had meningomyelocele, etc., as above. The latter 2 subsequently died.

Comment

Conduction anesthesia may be defined as the chemical interruption of sensory and motor nerve impulses by the use of local anesthetic agents. In obstetrics, this includes local infiltration of the perineum, pudendal block, lumbar sympathetic block, caudal block, lumbar peridural block, and spinal or subarachnoid block. Conduction anesthesia in obstetrics has two distinct advantages over general anesthesia:

1. The absence of respiratory depression and systemic effect in the fetus. Apgar and her co-workers[26] have shown statistically that infants are significantly less depressed with conduction anesthesia than with well-administered inhalation anesthesia.

2. The danger of maternal aspiration of vomitus is minimized since the mother may remain awake.

When proper sensory levels of conduction anesthesia are attained and pain relief is complete, the need for intrapartum sedation with narcotics and barbiturates, both of which cross the placenta in significant concentration to depress the fetus,[27] is diminished. However, chemical sympathectomy is associated with all of the major conduction anesthesia techniques such as spinal, caudal, and peridural anesthesia. Alterations in physiology associated with pregnancy[28] make the intrapartum patient particularly vulnerable to the effects of sympathectomy, especially hypotension and tissue anoxia.[29] These changes promptly alter fetal physiology and are often the cause of maternal as well as fetal death when not treated promptly with vasopressors and oxygen.[30-32] Many, if not most, of the fatalities associated with conduction anesthesia in obstetrics are the result of improper management after the block is complete.[33]

Minor conduction anesthesia. Local infiltration of the episiotomy site, pudendal block, and parasacral block, while adequate for delivery, do not relieve the pain of the first and second stages of labor. These blocks are frequently more time-consuming and have a higher failure rate than spinal anesthesia.[33] Lumbar sympathetic block is useful in the first stage but fails to ameliorate second stage discomfort and requires supplementation for the delivery of the infant. Paracervical block in combination with trichloroethylene, nitrous oxide, or other analgesics had proved effective in diminishing the pain of uterine contractions.[33] Cleland[34] reported successfully combining lumbar sympathetic block with low caudal anesthesia.

Caudal anesthesia. Hingson and Edwards'[35] description of continuous caudal anesthesia appearing in 1943 was enthusiastically received as the answer to labor and delivery. Twenty-four hour coverage of obstetrical divisions by experienced anesthesiologists have proved caudal analgesia to be a highly effective technique.[36, 37] It provides painless labor and delivery over an indefinite period when continuous technique is employed. It is particularly effective when there are medical conditions such as heart, kidney, metabolic, or pulmonary disease complicating the pregnancy. Technical difficulties associated with simple obesity, anatomical variations, and anomalies of the sacrum and sacral hiatus[38, 39] and lack of experienced anesthesiologists are among the causes of caudal failure. Drug reactions from the large amounts of drug used or too rapid absorption and the dangers associated with occult spinal puncture must be guarded against. Friedman[40] has shown that caudal block instituted too early in labor causes the labor to be slowed.

Spinal anesthesia. Spinal anesthesia utilizing the saddle block technique of Adriani and Roman-Vega[41] has stood the test of time as a safe and satisfactory technique in trained hands. It is simple, rapid, and more certain than most techniques, and it provides excellent pain relief for predictable duration. It does not affect the fetus. Complications occur rapidly and are of profound nature, affecting both mother and child, and are associated with hypotension and anoxia. These latter must be promptly reversed. Postspinal headache is more frequent in postpartum patients than in postsurgical patients.[33] Permanent neurological sequelae can occur, and spinal anesthesia has met with resistance on the part of the patient because of publicitiy of unfortunate results,[42, 43] although long-term follow-up series reported by Dripps and Vandam[44, 45] and by Dodge, Brown, and Jordan[46] have shown spinal anesthesia to be a benign procedure in trained hands. Continuous spinal anesthesia is not a desirable technique for obstetrical use.

Lumbar peridural anesthesia. Lumbar peridural anesthesia has been an accepted anesthetic technique for many years in general surgery[13, 14, 17] and has been successfully used in obstetrics,[15, 16, 21, 25] but the full potentiality of lumbar peridural anesthesia in obstetrics had not yet been appreciated. Lumbar peridural anesthesia has advantages for the intrapartum patient beyond the general advantages of conduction anesthesia previously stated:

1. Lumbar peridural anesthesia provides adequate analgesia and anesthesia for vaginal or abdominal delivery.

2. Lumbar peridural anesthesia may be made continuous by the insertion of a fine catheter into the peridural space which makes the level of anesthesia more controllable and places no temporal limitation, long or short, on the duration of the block. Since the catheter is not in contact with meninges, cord, or neural elements, as it is with continuous spinal anesthesia, the hazard of neurological sequelae, headaches, and cranial nerve palsy theoretically does not exist.[16]

3. Continuous lumbar peridural anesthesia may be kept segmental during the earlier stages of labor, blocking only the segments involved with painful sensation. This requires smaller volumes of drug to produce the same effect than with continuous caudal anesthesia, since the tip of the catheter is

placed nearer to the pain fibers and there is less possibility of drug reaction.

4. The block may be extended to provide anesthesia of the sacral segments for delivery of the infant and placenta and for episiotomy repair by placing the patient in semi-Fowler's position and adding drug slowly. This permits gravitational effect to bring the drug into contact with the sacral nerves.

5. Hypotension, nausea and emesis, and difficulty witih bladder and bowel are less frequent with peridural anesthesia than with spinal anesthesia according to Foldes and associates,[47] who feel that there is diminished severity of postanesthetic problems as compared to caudal and spinal anesthesia.

6. The incidence of successful block should approach 100 per cent. Bonica and associates[16] reported 6 per cent over-all failures; Foldes[47] recorded 5 per cent; Bromage[3] stated his failure rate to be 1.4 per cent. In this series, the failure rate was 2.3 per cent.

Continuous lumbar peridural anesthesia is a more difficult technique to master than spinal anesthesia and is also more time-consuming. Bonica,[33] however, stated that an operator equally dextrous with both techniques will have a lower incidence of failures with peridural anesthesia than with caudal anesthesia because of fewer anomalies in the lumbar spine than in the sacrum. The experience in this clinic confirms this statement.

The danger of occult spinal puncture and total spinal anesthesia is always present. As the catheter may also puncture the dura, a test dose and waiting period is mandatory. Both occult puncture and total spinal anesthesia may also occur with caudal anesthesia.

Summary

Lumbar peridural block has not attained popularity in obstetrical anesthesia although it has significant advantages for baby, parturient mother, and obstetrician. The use of continuous technique for long or short periods provides excellent anesthesia and good relaxation, and it does not affect the unborn child. The need for intrapartum barbiturates and narcotics is minimal or absent. Post–lumbar puncture headache does not occur. Lumbar peridural anesthesia is satisfactory for vaginal delivery or cesarean section. Complications are few and the success rate high in trained hands.

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Continuous caudal analgesia and anesthesia in obstetrics

A critical evaluation of 510 consecutive cases

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THE drawbacks of heavy intrapartum sedation with general or spinal anesthesia for delivery leaves much to be desired in the management of a private practice composed of a fairly high proportion of emotionally labile and sensitive patients. Since 1942 the method and technique of caudal anesthesia became an integral part of our obstetric management, and approximately 4,000 patients have been given this mode of therapy intrapartum by us. Anesthesiologists are called upon in our maternity department only to administer anesthesia for cesarean sections. Caudal analgesia was instituted as our preferred routine and was given to all patients except where definitely contraindicated. The failure rate has diminished as our skill in the procedure has increased.

Clinically we felt that the duration of labor was shortened, that postpartum hemorrhage was diminished, that the ease of operative obstetrics was increased by the considerable degree of perineal relaxation, and that there were no deleterious effects on the newborn infant. The satisfaction we have therefore had with intrapartum caudal analgesia has prompted us to continue its use up to the present time.

Caudal analgesia is relatively new in the field of medical anesthesia. Cathelin,[9] a French surgeon, first described the method in 1901. Since that time, numerous articles have appeared attesting to the value in pelvic diagnostic procedures and lower abdominal operations.[6, 7, 16, 18, 24, 26, 27, 31, 38, 43, 46, 48, 49, 51, 52, 54, 55] The development of the catheter technique of continuous administration increased its applications and safety.

In an evaluation of caudal analgesia it is essential to understand the neuropathways involved. The anatomy and neurophysiology of caudal analgesia in respect to childbirth have been described[10, 13, 15, 25, 34, 53, 58] and will not be reviewed here.

Material

The statistics and results presented are derived from a total of 631 consecutive cases, of which 510 were considered suitable by the 3 authors for attempted caudal analgesia. Thus, 80.8 per cent of all patients were candidates for caudal analgesia. If 36 cesarean sections for which hospital anesthesiologists were utilized are excluded, the corrected incidence of caudal analgesia given to patients is 85.7 per cent. The patient acceptance of caudal analgesia in our prac-

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tice has been almost unanimous so that very few have been denied this mode of analgesia because of personal reluctance or objection.

Technique of injection

The three authors were responsible for every caudal analgesia administered. The time of injection was determined solely by obstetrical criteria. Palpation of the caudal hiatus was accomplished at the time of anesthesia so that no patient was eliminated because of poor anatomical landmarks or obesity. Generally speaking, anesthesia was instituted when labor was well established and the presenting part engaged. Although various cardiovascular and pulmonary complications have been shown to be prime indications for intrapartum caudal analgesia, the majority of the cases presented are classified under "elective." Patients with breech presentations or twins were given this mode of analgesia after the criteria for the administration of caudal had been satisfied.

The method used for the administration of continuous caudal analgesia is begun with careful positioning of the patient in the left lateral position with the right thigh flexed on the abdomen and the left leg extended. A rigid 2½ inch 18 gauge needle* is introduced into the caudal canal and after the stylet is removed a 24 inch polyethylene catheter is threaded through the needle into the caudal canal. The needle is then withdrawn and 1.5 per cent Metycaine† is injected into the polyethylene tubing through a 23 gauge needle. The solution is introduced fractionally in 2 c.c., 6 c.c., and 22 c.c. doses at intervals so as to allow for possible sensitivity reaction or intrathecal administration. The catheter is then taped to the back and connected to the Metycaine solution by a rubber tubing to which a three-way stopcock and 10 c.c. syringe is attached so that closed circuit sterility is maintained. The patient is then able to lie on her back or in any comfortable position.

*Continuous caudal anesthesia needle, Becton, Dickinson & Co., Rutherford, New Jersey.

†Metycaine hydrochloride, Eli Lilly & Company, Indianapolis, Indiana.

Table I. Parity

Para	*No.*	
0	206	(40.4%)
1	191	
2	84	
3	23	(59.6%)
4	3	
5	2	
6	1	
Total	510	(100%)

Results

Caudal analgesia was administered to patients regardless of parity (Table I). The accepted criteria for its administration should not be inflexible in the hands of the experienced obstetrician. Forty per cent of our patients were primiparas and 60 per cent were multiparas. The patients with few exceptions were in active labor with the presenting part engaged or it could be pushed down to the spines by fundal pressure. The cervix should be partially effaced and at least 3 cm. dilated, and membranes are preferably ruptured. These findings are more often present in the primiparous patient than in the multipara who may fulfill these criteria without actually being in true labor. Lahmann,[33] in a series of 400 patients, had among them 368 primiparas. In the multipara, however, caudal analgesia may judiciously be given prior to engagement in the presence of good labor, ruptured membranes, absence of cephalopelvic disproportion or history of previous large babies.

In approximately one third of all the patients in this series labor was induced (Table II). These were elective inductions and consisted of amniotomy followed by intravenous Pitocin. There were no failures in this series of elective inductions and the longest labor in this category was 10 hours. One fetus weighing 1,786 grams died because of prematurity. These patients were carefully chosen, and the usual standards for induction were confirmed by vaginal

examination. When labor is induced caudal analgesia can usually be started at a much earlier dilatation than if the patient is admitted with spontaneous onset of labor. Cantarow,[8] in reporting 76 inductions following caudal analgesia, limited his patients to multiparas. In our series, labor was induced in primiparas but not as often as in multiparas. Caudal analgesia can be given before labor is induced. In 5 cases this was done with satisfaction. This requires constant attendance and is applicable to only a small percentage of patients in whom the cervix is very "ripe."

Although no control figures are presented here, the high incidence of stimulation of labor is apparent (Table III). Caudal analgesia, judiciously given, will not hinder normal labor, but occasionally the unengaged vertex will rise in station unless supplemental oxytocic agents are administered. It has been our practice to rupture the membranes artificially prior to or immediately following caudal analgesia if this has not occurred spontaneously.

Pitocin is administered in a large percentage of cases (75.8 per cent) and was given either before or after the injection into the caudal canal. When labor was not induced, Pitocin stimulation was given in 209 cases (62.8 per cent). There were no cases of ruptured uteri and in no case of Pitocin stimulation under caudal analgesia was cesarean section performed because of cephalopelvic disproportion. Obviously, a careful evaluation of each patient is mandatory. The intramuscular Pitocin noted in the early first stage represents that given to patients at time of soapsuds enema as a "priming" dose prior to elective induction of labor. No fetal or maternal complications arose in our series from the use of oxytocic

Table II. Onset of labor

	Primiparas		*Multiparas*		*Total*	
Onset of labor	*No.*	*%*	*No.*	*%*	*No.*	*%*
None listed			2*	0.4	2	0.4
Spontaneous	178	86.4	152	50.0	330	64.7
Rupture membranes with intravenous Pitocin	28	13.6	146		174	
Rupture membranes alone			1	49.6	1	34.9
Intravenous Pitocin alone			3		3	
Total	206	40.4	304	59.6	510	100

*Cesarean section.

Table III. Stimulation of labor

Stimulation	*No.*	*%*
No stimulation	83	16.2
Artificial rupture of membranes with Pitocin	304	59.6
Artificial rupture of membranes alone	41	8.0
Intravenous Pitocin for induction and stimulation	177	
Intravenous Pitocin stimulation early first stage	111	
travenous Pitocin stimulation late first stage	115	
ntravenous Pitocin stimulation second stage	107	75.8
Intramuscular Pitocin induction and stimulation	0	
Intramuscular Pitocin stimulation early first stage	73	
Intramuscular Pitocin stimulation late first stage	84	
Intramuscular Pitocin stimulation second stage	0	
Total	510	100

Table IV. Dilatation of the cervix at onset of caudal analgesia

Onset of caudal	*No.*	*%*
No dilatation	2*	
1 cm.	0	
2 cm.	23	50
3 cm.	66	
4 cm.	164	
5 cm.	77	28
6 cm.	66	
7 cm.	47	
8 cm.	42	22
9 cm.	12	
Full dilatation	11	
Total	510	100

*Elective cesarean section.

Table V. Hours under caudal analgesia

Hours under caudal	*No.*	*%*	*Caudal onset at or less than 4 cm. dilatation*		
			No.	*%*	
Less than 1	118	23.2	28	60.1	81.4
1-2	244	47.8	124		
2-3	88	16.1	54		
3-4	38	7.5	27	18.6	
4-5	17		17		
5-6	8		5		
6-7	2		1		
7-8	0	5.4			
8-9	0				
9-10	0				
Over 10	1				
Total	510	100			

Table VI. Influence of caudal on mechanism of labor

	No.	*%*
Occipitoanterior	340	66.7
Occipitotransverse	1	0.2
Occipitoposterior as such	1	0.2
Occipitoposterior anterior rotation	94	18.5
Occipitotransverse posterior rotation	0	0
Occipitotransverse anterior rotation	65	12.7
Frank breech	5	1.6
Full breech	1	
Footling breech	2	
Multiple pregnancy twins	1	0.2
Persistent occipitoposterior and transverse	124	24.3
Total	510	100

agents and caudal. However, the patients' clinical reaction to tumultuous labor or tetanic contractions under Pitocin stimulation is abolished once caudal analgesia has taken effect. Only 16.2 per cent of all patients completed labor without stimulation of any kind.

One of the most desirable advantages of caudal analgesia from the patient's point of view is that analgesia is initiated before full dilatation of the cervix or imminent delivery. Proper labor and no cephalopelvic disproportion remain our essential criteria for the administration of caudal analgesia. While some authors[45, 50] require at least 4 to 5 cm. dilatation before the institution of caudal analgesia 50 per cent of our patients received caudal analgesia at 4 cm. dilatation or less (Table IV). The 2 patients who were given caudal analgesia with closed cervices underwent elective cesarean sections. The complete abolition of pain in the first stage with no deleterious fetal effects is to be preferred to narcotic agents which, although relatively satisfactory, do not afford complete relief of pain. The greatest number of caudal analgesias were instituted at 4 to 5 cm. dilatation which agrees with most authors. Caudal analgesia given just prior to delivery at full dilatation still affords the patient and fetus the advantage of conduction anesthesia.

With use of the continuous catheter caudal analgesia technique, it is theoretically possible to continue analgesia for indefinite periods of time and in this series the longest duration of analgesia was 14 hours (Table V). Furthermore, the duration of labor is shortened under caudal analgesia because of its effect on the cervical circular musculature, birth canal, and floor of the perineum which allows more rapid dilatation and descent. In the total series taken at all levels of dilatation, deliveries occurred in less than 2 hours in 71 per cent of the patients. In Ritmiller's[47] series the average duration of caudal analgesia was 1 hour and 12 minutes. Other series[12] average as much as 5 hours. In a separate analysis of patients given caudal analgesia at 4 cm.

dilatation or less, over 60 per cent were delivered in less than 2 hours and over 80 per cent in less than 3 hours. The rapid softening and dilatation of the cervix following complete caudal effect occurs too frequently to be considered coincidental.[12]

The incidence of persistent occipitoposterior presentations has been found to be increased five times above the average.[39] Certainly this is unquestionably confirmed by Table VI, where in our series 124 out of 159 patients with occipitoposterior or occipitotransverse presentations at the time of administration of caudal analgesia required manual or forceps rotation to the occipitoanterior position prior to delivery. Lahmann[33] found only 7 persistent posterior presentations in 400 cases, but most of his caudal analgesias were given at full dilatation after many spontaneous rotations had already occurred. "Late" caudal analgesia resulted in only 17 per cent requiring rotation in Ritmiller and Rippman's[47] series. Lull and Hingson[37] found a little over 10 per cent persistent occipitoposterior and occipitotransverse presentations, while Nowill and Howland[44] found over 30 per cent. In our series, 24 per cent of all patients had persistent occipitoposterior or occipitotransverse presentations at delivery.

There is controversy as to the use of caudal analgesia in breech presentations. Some[32] consider it a contraindication, while others[37, 47] favor its use. Approximately one half of all patients with breech deliveries received caudal analgesia, usually at a somewhat more progressed dilatation than those with vertex presentations. Breech presentation does not preclude the use of caudal analgesia. It may be utilized very effectively after proper descent has occurred or even in the second stage as a terminal anesthetic. The use of caudal analgesia in multiple gestations has been described,[12] but the incidence in our series is too small to warrant comment.

Spontaneous rotation under caudal analgesia in the second stage of labor has been found by us to occur in less than one quarter of the cases, and then only after pro-

Table VII. Management of occipitotransverse and posterior

Manual flexion and rotation of head	114
Forceps rotation	10
Spontaneous rotation of occipito-transverse or posterior to anterior	35
Total	159

Table VIII. Method of delivery

Delivery	*No.*	*%*
Spontaneous	130	25.5
Low forceps	141	27.7
Mid forceps	229	44.9
High forceps	0	0
Assisted breech extraction	0	0
Total breech extraction	3	0.6
Breech decomposition and extraction	5	1.0
Low flap cesarean section	2	0.4
Total	510	100.1

Table IX. Total duration of labor (first and second stages)

	Primiparas		*Multiparas*		*Total*	
Hours	*No.*	*%*	*No.*	*%*	*No.*	*%*
0*	0		2		2*	
1	0		16		16	
2	7	32.6	68	75.0	75	57.1
3	24		76		100	
4	32		66		98	
5	32		23		55	
6	28	52.4	25	22.4	53	34.5
7	25		15		40	
8	23		5		28	
9	13		3		16	
10	11		0		11	
11	3		1		4	
12	1	17.0	1	2.6	2	8.4
13	3		2		5	
14	2		1		3	
16	1		—		1	
24	1		—		1	
Total	206	40.4	304	59.6	510	100

*Elective repeat cesarean section (no labor).

Table X. Intrapartum precaudal medication

Medication	*No.*	*%*
None	277	54.4
Barbiturates	32	45.6
Demerol	218	
Phenergan	204	
Trilene	1	
Total	510	100

longed labor (Table VII). This has prompted us to intervene earlier in the second stage and to effect delivery in the majority of cases by manual rotation of the head to the occipitoanterior position followed by elective forceps delivery. Manual rotation was accomplished digitally with 2 fingers and without displacing the head upward. Although the absence of resistance at the pelvic floor increases the incidence of persistent posterior presentations, the remarkable relaxation affords the obstetrician unexcelled ease in his operative maneuvers.

In most of the published data, the material deals mainly with position of the head at the time of delivery, method of delivery, and the incidence of successful analgesia. Twenty-five per cent of our patients were delivered spontaneously while the remainder required operative delivery (Table VIII). The latter were almost universally elective procedures if one may use that term in the absence of involuntary expulsive efforts by the mother. The spontaneous deliveries were effected by uterine contractions, maternal bearing-down efforts on direction of the obstetrician, or moderate fundal pressure. In our institution, the vertex must be in the direct occipitoanterior position with caput visible between contractions in order to be classified as low forceps. Forceps delivery of the head above this station has been termed midforceps in this series. The incidence of spontaneous delivery under caudal analgesia varies considerably in the literature from 15.8 per cent[37] to 44.4 per cent.[47] We suspect that variation may well be due to individual obstetrical preferences by the authors, since statistics with control series do not reveal an overwhelming increase in incidence of forceps with caudal.[11]

Primiparas unquestionably require more operative deliveries than multiparas,[11, 20] but this holds true with or without caudal analgesia. Our incidence of forceps deliveries (72 per cent) is comparable to that of Hingson[21] (78 per cent) and Lusk (65 per cent).[39]

The use of caudal anesthesia for cesarean section has been described elsewhere[2, 14, 17, 44] and was here used in only 2 cases. We are somewhat reluctant to use caudal analgesia in emergency cesarean sections because of its relatively prolonged onset of action and less effective visceral relaxation than spinal anesthesia. However, the 2 cesarean sections were elective and caudal afforded excellent anesthesia for the procedure. The catheters were left in situ and the incision was not made for 20 minutes so as to allow the full caudal effect. Additional Metycaine was given as required.

Some authors[21, 47] have shown that the total duration of labor under caudal analgesia does not differ statistically from that of a control series, and others[28] have indicated a considerable shortening in the first and second stages, particularly when the caudal analgesia is administered early in the first stage.

The duration of labor has been estimated by us to the nearest hour from the onset of regular contractions with effacement and dilatation of the cervix. When labor was induced, this was timed from the onset of the Pitocin infusion. More than 50 per cent of the patients in the series were delivered vaginally in 4 hours or less, with an over-all mean average of 4.8 hours (Table IX). The difference between primiparas and multiparas is apparent as would be expected. Excluded from the caudal series are those patients with frank or borderline cephalopelvic disproportion, some breech deliveries, and some cases of malposition in which the average labors were much longer. These are cases in which caudal analgesia is contraindicated.

Johnson[28] has demonstrated a decidedly beneficial action of caudal analgesia in cases of prolonged labor. Arthur and Johnson[3] have recommended its use in cases of cervical dystocia as 19 of 22 patients who had been in labor for an average of 44½ hours delivered under caudal analgesia in an average of less than 5½ hours.

Table X is presented to indicate that more than 50 per cent of the patients received caudal analgesia at about the time they customarily would have received parenteral or oral medication and that they

continued with painless labor. Thus, the absence of maternal and fetal depression from narcotic drugs is apparent in these alert mothers.

Sedation was administered shortly after admission to the labor room and before the administration of caudal analgesia. The patients in whom caudal analgesia was unsuccessful also received additional parenteral sedation. We feel that parenteral analgesia prior to administration of caudal analgesia should be given if required. This does not interfere with our evaluation since success in caudal analgesia implies to us complete abolition of all pain associated with labor.

Hingson and Edwards[24] reported 80 per cent complete effect with caudal. Later Lull and Hingson[37] had only a 12½ per cent failure rate with caudal analgesia. Mastroianni and associates[42] had only a 70 per cent success rate. In a series of cases of caudal analgesia given by members of a house staff[40] an 83 per cent success rate was obtained. Others, in presenting personal series, attained 85 to 90 per cent success.[11, 19, 32, 35]

Hingson[21] later still reported a 95 per cent success rate, while more recently Nowill and Howland[44] were 97.3 per cent successful. In the latter paper an additional 8 per cent required supplemental nitrous oxide at delivery.

There were 7 complete failures in our series, while in 6 others analgesia was unsatisfactory although perineal anesthesia for delivery was adequate (Table XI). Complete success was obtained in 97.5 per cent of our attempted cases. Included in the group of 19 patients who received nitrous oxide supplemental to successful caudal analgesia were those with incomplete analgesia, in addition to 13 other patients who, despite excellent anesthesia, insisted upon nitrous oxide gas at time of delivery because of personal fears, anxieties, and desire to be asleep.

The series of patients presented here represents the most recent 510 caudal analgesias attempted following 15 years of experience in this method by 2 of the 3 authors. With increase in skill and experience the number of patients with "poor" landmarks or prohibitive obesity has diminished and the outcome has been more successful. Criticism of caudal analgesia because of technical difficulties encountered cannot be justified by the fact that approximately 95 per cent of all the patients will undergo parturition painlessly and comfortably with no other mode of anesthesia. Proficiency in the palpation of landmarks and catheter technique can be achieved only by persistent personal application. The incidence of success and excellent anesthesia obtained justifies its use in every suitable patient.

Masters and Ross[41] showed that caudal analgesia eliminated precipitous labor and delivery and enabled the utilization of 100 per cent oxygen without the use of premedication and general anesthesia. They

Table XI. Evaluation of caudal analgesia, including cases requiring additional analgesia or anesthesia at delivery

Evaluation	*No.*	*%*	*Additional nitrous oxide and oxygen at delivery*		*Additional nitrous oxide, oxygen, and ether at delivery*	
			No.	*%*	*No.*	*%*
Successful analgesia and anesthesia	497	97.4	13	2.6		
Unsuccessful analgesia and anesthesia	7	1.4			7	1.4
Successful anesthesia						
Unsuccessful analgesia	3	1.2	6	1.2		
Partially successful analgesia	3					
Total	510	100	19	3.8	7	1.4

Table XII

Duration of pregnancy			*Maturity of newborn*			
Weeks pregnant	*No.*	*%*	*Weight in grams*	*No.*	*Weight in grams*	*No.*
32-33	3	0.8	1,600	1	3,200	62
34-35	1		1,800	2	3,300	59
36-37	14	2.7	2,000	1	3,400	29
38-39	264		2,100	1	3,500	28
40-41	211	3.3	2,200	4	3,600	21
42-43	16		2,300	5	3,700	16
44-45	1	93.2	2,400	6	3,800	10
Total	510	100	2,500	7	3,900	6
			2,600	17	4,000	3
			2,700	18	4,100	8
			2,800	41	4,200	1
			2,900	56	4,300	7
			3,000	39	4,400	1
			3,100	60	4,500	1

demonstrated its usefulness in the management of premature labor with a considerable reduction in neonatal mortality. In our series of 510 patients, 4 were delivered at 35 weeks or less while 27 infants weighed 2,500 grams or less at birth (Table XII). There were 3 neonatal deaths in this series with only one premature infant dying within 4 days of birth.

Contraindications and complications of caudal analgesia

We found that caudal anesthesia was unsuitable for 20 per cent of all our patients and that in those who were delivered per vaginam the incidence was 14.3 per cent. Severe obesity or anomalies of the sacral hiatus making introduction of the needle impossible are relatively infrequent. Acute infections in or near the sacrum are also seldom encountered but present an absolute contraindication. We have given caudal analgesia to patients in whom a pilonidal cystectomy has been performed. A history of central nervous system disease or mental disturbances will deter our using caudal analgesia on purely medicolegal grounds, even if no valid organic contraindication exists. Patients with borderline or cephalopelvic disproportion are not given conduction anesthesia, as it may impair a proper and thorough trial of labor. A patient with antepartum hemorrhage or any obstetrical complication which may produce a shock-like state is not given caudal analgesia because the moderate hypotensive effect may aggravate the situation or cloud the clinical picture.

Hingson and others[23] found that newborn mortality and morbidity with continuous caudal analgesia were due to fetal anoxia resulting from hypotension, prolonged labor because of increased persistent occipitoposterior presentations, and fetal sensitivity to the anesthetic agents. However, the neonatal deaths and delayed onset of respiration in full-term or premature infants were statistically diminished under caudal analgesia as compared to a control. In our series of 510 cases there were 3 neonatal deaths. Two infants died in the immediate postpartum period of congenital anomalies inconsistent with life (ruptured omphalocele and congenital heart disease). A third premature infant died 4 days after delivery.

The series under consideration here is too small to evaluate statistically the incidence of the various complications of caudal analgesia. Massive intradural injection of the anesthetic agent remains the single most serious accident. The dose of the agent approximates four times that which would accomplish a similar level with spinal block. Accidental injection into the spinal canal occurred twice in our series and should actually be classified as a contraindication rather than a complication. The emergence of spinal fluid upon removal of the stylet of the needle, or a spinal effect following a proper waiting period after an initial introduction of a "spinal" dose of Metycaine, should produce sufficient warning of this serious condition. Nitrous oxide–oxygen anesthesia preliminary to institution of caudal analgesia making a "test dose" impossible is mentioned only to be unequivocally condemned.[30]

Hypotension following caudal analgesia is perhaps the most common adverse reaction. The incidence has been variously reported from 4 per cent[12] to 20 per cent.[24] Hingson and Edwards[24] have stated that

"blood pressure falls have been in direct proportion to the anesthetic efficiency of the drug and are apparently due to the pharmacological effect of producing splanchnic and lower extremity peripheral vasomotor block." In this series,[24] if the level was not above the umbilicus, less than 8 per cent had blood pressure drops of more than 20 mm. August[4] found that 78 per cent of the patients had an average drop in systolic pressure of 14.6 mm., and 73 per cent had an average diastolic drop of 13.2 mm. Treatment of severe hypotension with Trendelenburg position, oxygen and ephedrine or other vasopressor agents must be used if necessary.

The use of the catheter technique has obviated needles broken in the caudal canal. After the catheter has been introduced through the needle into the caudal canal it should never be withdrawn with needle in situ as it may be cut by the beveled edge of the needle. This can be avoided by withdrawing the needle first and then the catheter.

Urinary retention requiring 4 or more catheterizations occurred only three times in our series. Others[21, 24] have shown no increased incidence in catheterization following caudal analgesia, and Downing[11] demonstrated a decreased incidence in urinary retention. Loss of anal sphincter tone for up to 6 weeks has been described.[12] This complication, lasting 3 weeks, occurred on one occasion prior to the collection of this series. Spontaneous return of sphincter control was complete after 3 weeks.

Generalized tonic and clonic convulsions following introduction of the anesthetic agents are rare but did occur once in 510 cases. This was probably due to accidental intravenous administration of the drug or exceedingly rapid absorption. Vertigo and tinnitus are not infrequent after the initial caudal injection and are also due to intravascular absorption, but these symptoms subside quickly without therapy and leave no sequelae. A grossly "bloody" tap either should discourage further attempt at caudal analgesia or an effort may be made to replace the needle to a more favorable position thereby avoiding rapid intravascular introduction of the drug.

Sensitivity to cocaine derivatives and even anaphylactic shock has been described with anesthetic agents in caudal analgesia.[1] Fortunately, this is exceedingly rare and was absent in our series. Inquiry into a history of sensitivity to local anesthetic agents is essential, and a number of patients were excluded because of previous reaction. The initial fractional sensitivity dose in caudal technique should always be observed even in the absence of such history.

Other complications occasionally attributed to caudal analgesia are damage to nerve routes[19] and extradural infection.[44] These were not encountered although one subcutaneous abscess resulted recently following failed caudal analgesia in an extremely obese patient where the sacral canal was never entered. This responded well to incision and drainage.

Comment

Caudal analgesia permits continuous complete intrapartum analgesia with the absence of significant side effects or complications in the normal case. When there are certain complications of labor this type of analgesia is also indicated.

The absence of pain and subsequent reduction in anxiety and apprehension without narcotics has led to the recommendation of caudal analgesia for patients with congenital or acquired heart disease, tuberculosis, and other pulmonary complications.[14, 35, 45, 56] Fractional administration of medication is advised in these cases in order to avoid precipitous hypotension.

The usefulness of caudal analgesia in cases of prolonged labor has been evaluated. Ball and Chambers[5] utilized it successfully in cases of primary cervical dystocia indicating a possible disturbance of the neuromuscular mechanism rather than a purely mechanical obstruction. Johnson and Clayton[29] using radioactive sodium, demonstrated a general reduction of placental circulation in cases of prolonged labor, which in some cases may be as low as 50 per cent of the normal mean

value. They stated that "continuous caudal analgesia results in the demonstrable improvement in placental action, presumably from a direct vasodilatation effect on the decidual vessels."

A considerable reduction of bleeding following the third stage of labor occurred in our series as well as in others.[59] Five patients suffered a postpartum blood loss of 500 c.c. or more. Of these, 2 were delayed hemorrhages on the sixth postpartum day, and curettage revealed only necrotic decidual tissue. One patient bled from a traumatic laceration of the vaginal vault and another from a retained placental fragment. There was only one case of persistent postpartum uterine atony resulting in excessive hemorrhage. The latter was controlled with oxytocic agents and blood transfusions. Vaux and Mitchell[59] have indicated a shortening of the third stage with caudal analgesia stating that "it is believed that continuous caudal analgesia and anesthesia in obstetrics enables the uterus to approximate its normal mechanism more closely." Thorpe[56] suggested its use at full dilatation of the cervix with marginal placenta previa where the patient was not in shock or was not bleeding profusely.

Caudal analgesia has resulted in diminished fetal mortality in premature births,[21, 22] normal births,[36] and breech presentations.[22, 57] Lull[36] found no Metycaine in the amniotic fluid studied at the time of cesarean section in a patient who had been given caudal analgesia.[21]

The obstetrician utilizing caudal analgesia should be intimately acquainted with its technique, physiology, possible complications, and side effects. He should be prepared for the increased use of oxytocic agents in labor and be ready to terminate labor electively in cases where the occiput remains in the posterior or transverse position. In gaining familiarity with this mode of analgesia and anesthesia, he will be rewarded by increased patient acceptance as well as by unexcelled anesthesia for labor and delivery, together with a reduction in fetal mortality.

Summary

1. Five hundred and ten patients in whom caudal analgesia was attempted were studied.
2. Eighty per cent of patients in labor were found to be suitable for caudal analgesia with 97.5 per cent complete success.
3. An increased incidence in the use of oxytocic agents and operative obstetrics was found.
4. The advantages of caudal analgesia with elective induction of labor are stressed.
5. Three babies were lost, of whom 2 had congenital abnormalities incompatible with life. This gives a corrected neonatal mortality rate of 0.2 per cent.

We wish to express our thanks to Drs. Louis M. Hellman and Edward Solomons for their help in the preparation of this paper.

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Therapeutic abortion and sterilization committee

A 3 year experience

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EVERY practitioner of medicine in any specialty is occasionally confronted with an absolute need for the therapeutic interruption or prevention of pregnancy. Since therapeutic abortion results in the destruction of life and sterilization prevents the initiation of life, both of these procedures must be considered contrary to ideal medical practice which is dedicated to the preservation of life. Neither the legal nor the medical profession has clearly outlined the procedure to be followed when the physician is impelled to present urgent indications for these measures. As is true in most states of this country,[1] the state of New Jersey[2] has been equally lax in clearly stating a legal code to be used by the medical profession in such therapeutic measures. There is no statute covering any aspect of the legality of sterilization. The performance of a therapeutic abortion in New Jersey is legally acceptable if not done "maliciously or without lawful justification."[2] The burden of proof to sustain such a decision is not definitely placed on the legal prosecution or on the medical defense. By custom only, medical practice has accepted certification of necessity when the case history has been attested to by either 2 or 3 legally licensed physicians in the state of New Jersey.

The absence of a clearly defined legal code and the inadequacies of medical custom in the perplexity of therapeutic abortion and sterilization necessitated the establishment of a Therapeutic Abortion–Sterilization Committee to adjudicate these problems. The establishment and work of this Committee at Newark Beth Israel Hospital for the years 1956 through 1958 is the subject matter of this report.

In casting about for a better plan of operation, reference was made to the discussions of Pearse and Ott[3] and Guttmacher[4] regarding the establishment of a nonpartisan committee to evaluate all aspects of therapeutic abortion and sterilization to be done within the hospital. From these patterns evolved the following plan. The Executive Director of the Newark Beth Israel Hospital was made the permanent chairman of a committee composed of 10 physicians, certified diplomates of the American Board of Obstetrics and Gynecology. The consultative opinion of various members of different medical specialties was obtained whenever indicated in problems not wholly concerned with obstetrics and/or gynecology. To maintain impersonal objectivity, the medical members of the committee were known only to the permanent chairman. Requests for therapeutic abortion or sterilization were processed as follows:

1. A letter of request, originating from any member of the medical staff, was submitted, together with all documentary indorsement, to the office of the Executive Director of the hospital.

2. A pertinent abstract of the request, less the identity of the patient and the requesting physician, was prepared. The identity and

From Beth Israel Hospital.

opinion of the substantiating consultant or consultants were retained in the abstract.

3. This abstract was submitted by the Executive Director to 4 members, at random, of the 10 member committee for approval or disapproval. Since the identity of the members polled was not revealed for any reason, judgment passed was independent at all times. Any member polled might delay his decision for further information or documentation but ultimately submitted his final opinion.

4. Approval of 3 members of the 4 polled was required for permission to carry out a request. When this was obtained, the Executive Director notified the requesting physician and the supervisor of the operating room that such permission had been granted.

5. When permission was denied by the first 4 physicians polled (at least 2 men disapproving), the requesting physician could apply for a canvass of the entire 10 member committee. In such action, indorsement had to be given by 7 members for permission to perform the procedure.

Material studied

During the period covered in this study (1956-1958), there were 272 requests for permission to perform therapeutic abortion and/or sterilization. Of these, 37 (13.6 per cent) arose from the ward patients and 235 (86.4 per cent) originated from the private services.

The age distribution of the petitions handled (Table I) ranged from 15 years to over 40 years, with the majority in the 20 to 39 year bracket. This is comparable to figures reported by the Mayo Clinic.[5] Therapeutic abortions alone were approved and done in all age groups with the predominant number (48.1 per cent) in the 30 to 34 year group. Therapeutic abortions with sterilizations were predominant among the individuals in the fourth decade. No sterilization requests were received in the teen-age group. The bulk of the salpingotomies were performed in the 25 to 39 year age group (60.8 per cent).

A summary of the action taken by the Committee is shown in Table I, wherein 48 requests for therapeutic abortions alone resulted in 35 approvals and 13 rejections. It is worthy of note that in 4 instances, despite committee approval, no abortion was carried out. In 15 cases in which permission to perform therapeutic abortion and sterilization was requested, approval was unanimous and the procedure executed. Sterilization proposals accounted for 209 applications, with 205 accepted, of which 65 were not enacted. The Committee disapproved the criteria of indication in 4 applications.

There were 10,874 patients delivered in the Newark Beth Israel Hospital in 1956-1958. A correlation of the 46 patients who were aborted for therapeutic reasons to the total number of deliveries disclosed an incidence ratio of 1:236. The 140 sterilizations performed yielded an incidence ratio of 1.28

Table I. Age distribution and disposition of requests

	Request and disposition						
	Therapeutic abortion			*Therapeutic abortion and sterilization approved and done*	*Sterilization*		
Age	*Approved and done*	*Approved and not done*	*Not approved*		*Approved and done*	*Approved and not done*	*Not approved*
15-19	5	0	0	0	0	0	0
20-24	3	0	2	1	12	8	0
25-29	5	1	3	1	43	18	1
30-34	14	2	4	6	45	22	2
35-39	3	1	3	3	39	15	1
40-	1	0	1	4	1	2	0
Total	31	4	13	15	140	65	4

Table II. Therapeutic abortions by indications approved for intervention

Indication	*Therapeutic abortion alone*		*Therapeutic abortion and sterilization*	
	No.	*%*	*No.*	*%*
Neuropsychiatric	15	42.86	2	13.33
Cardiovascular, total	9	25.71	7	46.68
Rheumatic heart disease	4		4	
Hypertensive vascular disease	3		2	
Arteriosclerotic heart disease	1		0	
Ruptured aneurysm	1		0	
Coronary disease	0		1	
Renal disease	0		2	13.33
Tuberculosis	0		2	13.33
Rubella	5	14.29	0	
Others, total	6	17.14	2	13.33
previous carcinoma	1		1	
Rh problem	1		1	
Toxic thyroid	1		0	
Retinoperivesiculitis	1		0	
Acute bleeding colitis	1		0	
Best's disease	1		0	
Total	35	100.00	15	100.00

per cent of the number delivered. Despite the fact that the general considerations of these problems are similar, detailed analysis of therapeutic abortion with or without sterilization as against sterilization alone will be presented separately.

Analysis of the therapeutic abortions

Applications for therapeutic abortion were handled as individual problems by the Committee. No automatic approvals or standard indications were recognized by the Committee. Each situation was circularized for evaluation and judgment. The approved indications for 35 therapeutic abortions fell into three major groups: the neuropsychiatric group (42.86 per cent), the cardiovascular group (25.71 per cent), and rubella (14.29 per cent). In addition to these groups there were a miscellany of single indications (Table II).

In 4 of the 35 approved cases, therapeutic abortion was not carried out. Two of these 4 patients disappeared after approval and no follow-up was possible. One patient, a gravida i, whose case was approved for therapeutic abortion on a psychiatric basis, underwent curettage for spontaneous incomplete abortion. The fourth patient, whose case was approved for therapeutic abortion on a psychiatric basis, refused interruption and was delivered at term. On the basis of grand multiparity and hypertension she was sterilized post partum.

The indications not approved for therapeutic abortion (Table III) were generally inadequately documented for the stated indication. The psychiatric requests included 3 "pre-psychotic personalities" in primigravidas under 25 years of age. One psychiatric patient was a 40-year-old gravida v, para iv, who threatened suicide. The opinion was that such feelings were often verbalized by many women having an undesired pregnancy. Two patients were presented as having a "depressive fear" of pregnancy and the psychiatric situation was judged too superficial to warrant intervention.

The 3 cardiovascular patients for whom abortion was not approved failed to have substantial evidence to indicate the need for interruption. The 2 cases of rubella, one at 6 weeks' and one at 9 weeks' gestation, were not objectively observed by a physician. The case of Rh isoimmunization was in a gravida iii, para ii, who had had 2 previous erythro-

blastotic babies, neither of which survived. Upon carrying this pregnancy to term she was delivered of a macerated erythroblastotic stillborn infant. When this result was brought to the attention of the Committee it was felt that more earnest consideration should be given Rh problems in the future. The case of pernicious vomiting was not considered serious enough to allow interruption; no follow-up information was available.

The accepted indications for therapeutic abortion along with sterilization (Table IV) were similar to those for therapeutic abortion alone, with the addition of permanence and irreversibility. In the largest group, cardiovascular, there were 4 patients with various manifestations of serious rheumatic heart disease. The hypertensive patients were multiparas with residual effects from recent toxemia. The patient with coronary disease was a 44-year-old gravida iv, para iii, with clinical and electrocardiographic evidence of coronary insufficiency.

The 2 patients whose cases were approved for interruption and sterilization for psychiatric indications included one who had a severe persistent anxiety neurosis and one with a suicidal depression with actual attempted suicide. The 2 cases approved in this group because of renal disease included a patient 39 years of age with recurrent pyelonephritis after the birth of 7 living children.

The 2 patients with tuberculosis whose cases were approved for interruption and sterilization included one 32-year-old patient, a gravida iii, para ii, with contralateral recurrence of tuberculosis after a thoracoplasty. The other case of tuberculosis was in a 33-year-old patient with 3 living children and extensive active disease.

A total hysterectomy and bilateral salpingo-oophorectomy was performed at 7 weeks' gestation in a 35-year-old woman, gravida iv, para iii, in whom a radical mastectomy for carcinoma had been performed 18 months previously, in the thirty-sixth week of her prior pregnancy.

The patient with Rh isoimmunization was a 30-year-old para iii, with erythroblastosis in each of the 3 newborn infants, the first 2 surviving. She was, in addition, under psychiatric care for severe psychoneurosis.

Analysis of the sterilizations

Among the 209 requests which came before the Committee for primary operations for sterilization, 38 arose from the ward patients and 171 from the private service. During the early months of 1956, when the Committee was first established, all operations resulting in sterility during the childbearing age were brought before the Therapeutic Abortion and Sterilization Committee. The large volume of material so involved soon proved to be beyond the scope of the Committee. This matter was justly placed under

Table III. Indications not approved for therapeutic abortion

Indication		*No.*
Neuropsychiatric		6
Cardiovascular, total		3
Rheumatic heart disease	2	
Hypertensive heart disease	1	
Rubella		2
Rh problem		1
Pernicious vomiting		1
Total		13

Table IV. Comparison of indications approved for sterilization

Indication	*Present study*		*Pearse and Ott*[3]	*Prystowsky and Eastman*[6]	*August*[7]
	No.	*%*	*(%)*	*(%)*	*(%)*
Grand multiparity	106	51.71	5.0	33.28	13.3
Repeat cesarean section	74	36.10	15.1	15.35	6.3
Previous gynecologic operation	10	4.88	24.5	1.97	6.3
Cardiovascular	9	4.38	22.5	22.67	3.2
Tuberculosis	1	0.49	2.7	3.72	1.4
Blindness	1	0.49	0	0.55	0.3
Others	4	1.95	30.2	22.46	69.2
Total	205	100.0	100.0	100.00	100.0

the jurisdiction of the Tissue Committee of Newark Beth Israel Hospital, established and functioning according to the requirements of the Joint Commission on Accreditation of Hospitals. Such matters were adjudicated by this committee for operative indication, tissue justification, and related considerations.

A statistical breakdown of the indications accepted for sterilization compared to those of other institutions in the country[3, 6, 7] is presented in Table IV. Grand multiparity and repeat cesarean section accounted for 87.8 per cent of the total number of sterilizations. These indications for sterilization were accorded "routine approval," granted by the Executive Director without circularizing the Committee. Such permission was forthcoming when documented evidence was presented in the following situations:

1. A multigravida who had been delivered of 7 or more children. This type of request accounted for application and approval in 106 instances (51.71 per cent).

2. Sterilization to be performed at the time of the third or subsequent cesarean section, upon the request of the operating surgeon and signed approval of both parents. Fifty-two such requests were approved. At the time of a second cesarean section, approval by the Committee would follow if an application, sincerely instigated by both parents through the operating surgeon, was made. Such a matter of parent initiation was judged satisfactory in 22 instances. In all, this indication accounted for 36.10 per cent of the total sterilizations.

Interdiction of pregnancy for the protection of reconstructed perineal relaxations by plastic gynecologic operation drew Committee approval in 10 cases, especially when the permanent alteration in fecundity was a secondary procedure. Similarly, advanced parity of 5 or more was an influencing factor in the acceptance of the above and cardiac group indications for sterilization. Patients suffering from the residuals of hypertensive heart disease or from advanced rheumatic heart disease were approved for salpingotomy as a primary operation in 7 instances. After close scrutiny, best maternal welfare was judged to be served by interruption of fertility in one case each of the following conditions: tuberculosis, retinoblastoma, carcinoma of the breast, carcinoma in situ of the cervix, Rh isoimmunization, and residuals of poliomyelitis.

In 65 cases, sterilization was approved by the Committee but the procedure was not carried out during the years studied. The indications for this group followed the pattern for all the material. Over one half of these grand multiparas refused sterilization in the immediate postpartum period. The initial fear of pregnancy was eliminated once the patient had been successfully delivered and a refreshed outlook for the future made these patients seek contraceptive advice rather than a permanent alteration in their reproductive capacity. The refusal at the time of repeat cesarean section was occasioned most often by the disappointment in the sex of the newborn child and consideration of another try was universal when the operator could give the mother assurance of the safety of another delivery by the abdominal route. The 3 patients with severe hypertensive disease posed the most difficult problem since the supervising physician judged the risk of elective operation to be too great for the patients' precarious cardiac balance. It was most gratifying to us to see such individualization carried out so thoroughly. In two instances of approved sterilization for previous plastic procedures, the precipitous events of immediate delivery after admission to the hospital obviated the need for cesarean section. Hence, the realization that subsequent pregnancy posed no additional threat to the perineal integrity of these patients removed the consideration for any postpartum operation. It was also noteworthy that the ward patients twice as often refused postpartum sterilization as did the private group.

The views and policies of the Committee were widely distributed so that refusal for sterilization was decided in only 4 of the 209 applications. In 3 grand multipara, the incidence of delivery was great enough but the fetal survival rate was lower than 5 so that those patients did not meet Committee

Table V. Comparison of ratio of therapeutic abortions and sterilizations to deliveries

Source	*Therapeutic abortions*			*Sterilizations*		
	Period	*No.*	*Ratio to deliveries*	*Period*	*No.*	*Per cent of deliveries*
Bellevue Hospital[8]	1935-45	199	1:76	--	--	--
University of California Hospital[9]	1942-48	58	1:88	--	--	--
New York Lying-In Hospital[10]	1932-43	280	1:167	--	--	--
Iowa University Hospital[11]	1926-50	137	1:176	--	--	--
Chicago Lying-in Hospital[12]	1949-54	301	1:901	--	--	--
Mayo Clinic[5]	1945-54	64	1:223	--	--	--
Los Angeles County Hospital[13]	1931-50	295	1:285	--	--	--
367 hospitals in U.S.A.[14]	1941-50	2,717	1:418	--	--	--
Boston Lying-in Hospital[15]	--	--	--	1916-49	1,106	1.7
Philadelphia Lying-In Hospital[16]	--	--	--	1924-49	1,550	3.0
Hackley Hospital, Mercy Hospital[7] (Muskegan, Michigan)	--	--	--	1944-54	606	3.3
Present study	1956-58	46	1:236	1956-58	140	1.28

standards of 7 living offspring which was established at the time of inception of this plan. One case of labile hypertensive disease in a gravida v with mild toxemia in the last 2 deliveries did not have consistently demonstrable vascular involvement after interval examination by an appointed specialist in internal medicine. Hence, the refusal of one of 52 applications for sterilization is slightly lower than the 12 refusals of 72 reported by Pearse and Ott.[3]

Comment

The plan of operation of the Therapeutic Abortion–Sterilization Committee has been found to be effective and impartial. It is our opinion that the successful operation of a plan such as herein described is dependent upon the widest dissemination possible of the policy of the Committee.

The incidence of therapeutic abortions to deliveries (1:236) and the sterilization ratio (1.28 per cent) compares favorably with reported figures throughout the country[5, 7, 8-16] (Table V).

The two principal indications for interruption of pregnancy in this series, neuropsychiatric illness and cardiovascular disease, were also prominent indications in other reported series[1, 5, 12, 14] (Table VI). The high rate of approval for neuropsychiatric indications at Beth Israel Hospital as well as in the

Table VI. Comparison of indications approved for therapeutic abortion

Indication	*Present study (%)*	*New York City[1] 1951-1953 (%)*	*Mayo Clinic[5] (%)*	*Chicago Lying-in Hospital[12] (%)*	*367 hospitals in U.S.A.[14] (%)*
Neuropsychiatric	42.86	37.8	17.0	15.0	14.87
Cardiovascular	25.71	15.7	14.0	26.0	15.46
Tuberculosis	0	8.7	9.0	0	9.57
Rubella	14.20	3.4	0	7.0	0.96
Rh problem	2.86	1.5	0		0.96
Previous carcinoma	2.86	2.9	13.0	0	0.62
Toxic thyroid	2.86	1.5	0	0	0
Toxemia of pregnancy	0	2.6	17.0	0	2.65
Renovascular	0	0	0	26.0	13.79
Others	8.65	25.9	30.0	26.0	41.12
Total	100.00	100.0	100.0	100.0	100.00

New York City series[1] points up the similarity of thinking and judgment regarding these problems in the metropolitan area. The absence of neuropsychiatric indications among the approved sterilizations in this study came about because of the disseminated intent of the Committee to accept this indication only after prolonged observation of such patients by trained psychiatrists.

The consideration of cardiovascular disease as an indication for therapeutic abortion and/or sterilization was dependent upon the evaluation of the involvement and the residuals.

The acceptance of 7 living children (grand multiparity) as an indication for sterilization was decided upon by the Committee only after most vigorous discussion; nevertheless, this indication showed the highest incidence (51.71 per cent) in this series (Table IV). It is believed that this best meets the needs at our institution. The occurrence of a sterilization incidence of 36.10 per cent for repeat cesarean section was occasioned by the adherence of most of our staff to the dictum "once a section always a section." This attitude is prompted by the absence of operating facilities for abdominal delivery on our labor and delivery floor.

The rubella and Rh problems which comprised 17.06 per cent of the accepted indications for abortion were not represented in similar magnitude elsewhere, probably because this study is chronologically later.

The 12 miscellaneous indications in the entire survey are single situations which will vary with the numerical size, the socioeconomic background, and the local requirements of any particular segment of the population. As a general rule the Committee felt that patients would be eligible for sterilization only because of such organic diseases as would make them worthy of consideration for therapeutic abortion.

The indication and documentation of a request for therapeutic abortion and/or sterilization must be most carefully evaluated. The individual physical and mental responses of the patient to the continuation or interruption of the pregnancy must be carefully weighed. The feeling of guilt after interruption of a pregnancy or a sterilization may create a far more serious, permanent problem than would have been created by permission of continuation of the pregnancy or failure to sterilize the patient. It would seem almost advisable to have psychiatric evaluation of every patient in whom therapeutic abortion and/or sterilization is contemplated to ascertain the stability of the individual and her capacity to accept the performance of either act. Thus, it is urged that the evaluation of the problem at hand, and its solution, be weighed against the possible conflicts which may be created.

Summary

The urgent need for, the organization of, and the review of the first 3 years' function of the Therapeutic Abortion–Sterilization Committee at Newark Beth Israel Hospital have been presented. The disposition of the 272 requests for permission to perform therapeutic abortion and/or sterilization has been analyzed. The performance incidence of therapeutic abortions (1:236 deliveries) and sterilizations (1.28 per cent of the number of deliveries) compares favorably with the figures quoted from other large series. The impartial, anonymous, efficient performance of this Committee permits complete recommendation of such an organization to handle the requests for therapeutic abortion and sterilization at any hospital.

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The problem of spontaneous abortion

VIII. Stillbirth

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THE similarity between the histological and serological patterns found in the placental villi and maternal serum in cases of spontaneous abortion and prematurity,[1, 2] suggested that it might be profitable to extend our inquiry in order to see if this apparent correlation embraced stillbirth as well.

The histological changes in the placental villi from cases of spontaneous abortion and prematurity consist of a gradation of lesions beginning first, with metachromasia of the ground substance, then Hofbauer and stromal cell proliferation, later foci of fibrinoid necroses, and, last, complete intravillous collagenization with partial to complete ablation of vascularity. It is only in the final stage that the villous epithelium shows evidence of damage—usually in the form of atrophy.

Since the histological changes in the villi resembled those seen in "collagen disease," a modified Rose-Waaler test was made on the serum from cases of spontaneous abortions and premature delivery. A significant number were positive, confirming the assumption that these complications of pregnancy came into the general group of the collagenoses.

Methods and materials

The placental villi from cases of stillbirth were examined by methods already described.[3, 4] The Rose-Waaler estimations were made on the maternal serum from blood taken at the time of birth in a manner previously reported.[1, 2] The patients were not selected but were taken in the order of admission to hospital.

Control Rose-Waaler titers in normal pregnancy have previously been shown in some detail.[1, 2] They have now been extended to cover 138 women in the various stages of pregnancy. A normal limit was found in 137; one had a pathological titer for which no cause could be found at that time. Unfortunately, she was not followed after delivery.

Results

Table I shows the Rose-Waaler titers, the placental villous changes, and the complications found in 30 cases of stillbirth.

Seventeen showed an abnormal Rose-Waaler titer combined with pathological lesions in the placental villi. In another 8 there were proliferative villous lesions with a normal Rose-Waaler reaction; in one case there were normal villi but an increased serum titer. In 4 cases (Cases 2, 5, 15, and 23) the cause of fetal death could possibly be ascribed to toxemia, maternal age, obstetrical manipulation, and placenta previa. In this latter group both the villi and the Rose-Waaler level were normal.

Among other complications were 6 cases of toxemia of pregnancy, one of a normal serum and an infarcted placenta, and 5 of proliferative villous changes, 3 of which included an increased Rose-Waaler titer.

Three babies had gross congenital malfor-

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This work was supported by a Federal Health Grant.

mations, one showed both a pathological placenta and titer, another a normal placenta and titer, and the third a raised titer and an apparently normal placenta.

An analysis of the figures shows that approximately 57 per cent of the group had both villous lesions and abnormal titers, another 26 per cent pathological villi and normal serological findings. The total showing one or both stigmas was 86 per cent.

If the primipara, the patient who underwent forceps delivery, and the one who had placenta previa are removed from the group, 12 of the remaining 20 patients have histories of abortion, prematurity, or stillbirth; that is, 60 per cent of the total number. In a series of premature births studied in the same way the incidence was 70 per cent.[2]

Comment

The placental villous lesions present in our cases of stillbirth are identical with those

Table I

Case No.	Parity	Rose-Waaler titer C	Rose-Waaler titer T	Villous histology	Remarks
1	3	0	1:4	Completely collagenized	1 previous abortion; 1 full term
2	Primipara	0	1:8	Massive areas of white infarction	Toxemia of pregnancy
3	Primipara	0	1:64	Stromal hyperplasia	———
4	1	0	1:4	Completely collagenized	Previous pregnancy normal
5	Primipara	0	1:8	Normal	Anencephalic baby, mother aged 14
6	Primipara	0	1:16	Stromal proliferation; fibrinoid plaques	———
7	6	0	1:32	Completely collagenized	Previous pregnancies normal; this one mild pretoxic state
8	4	0	1:32	Completely collagenized	1 premature, 1 abortion, 1 stillbirth
9	3	0	1:32	Stromal proliferation	2 previous full term; pre-eclampsia
10	2	0	1:64	Stromal proliferation	1 previous abortion
11	Primipara	0	1:128	Completely collagenized	———
12	6	0	1:64	Normal	1 previous abortion, 4 full term; this baby has spina bifida
13	2	0	1:16	Completely collagenized	1 stillbirth (congenital malformation); this baby anencephalic
14	3	0	1:32	Stromal proliferation	2 normal births; this one cord around neck
15	14	0	1:4	Normal	Forceps delivery; previous pregnancies normal
16	Primipara	0	1:64	Completely collagenized	Rh negative
17	5	0	1:8	Completely collagenized	1 abortion; 1 stillbirth; 2 normal; blood for RW taken 3 days after delivery
18	Primipara	0	1:128	Metachromasia	Mildly toxic
19	5	0	1:4	Completely collagenized	4 previously normal; hypertension
20	1	0	1:16	Hyalinized; epithelial atrophy	?
21	6	0	1:32	Stromal proliferation	3 normal; 1 abortion; 1 premature
22	2	0	1:2	Completely collagenized	1 normal
23	3	0	1:4	Normal	1 abortion; 1 stillbirth; present pregnancy complicated by placenta previa
24	2	0	1:4	Completely collagenized	1 previous stillbirth
25	4	0	1:32	Hyalinized, epithelial atrophy	1 stillbirth; 2 normal
26	10	0	1:4	Stromal proliferation	1 premature; 8 normal; mildly toxic
27	17	0	1:128	Metachromasia	2 stillbirths; 4 normal
28	4	0	1:32	Stromal proliferation	3 normal; cord around neck
29	Primipara	0	1:4	Hyalinized with epithelial atrophy	———
30	6	0	1:32	Stromal proliferation	2 premature; 3 normal

found in spontaneous abortion and prematurity. The Rose-Waaler titers in the maternal serum for a respectable number of the stillbirth series have been shown to give increased levels similar to the findings in prematurity[2] and abortion.[1]

The incidence of one or both stigmas in spontaneous abortion was 75 per cent,[1] in prematurity 84 per cent[2] and in this series 86 per cent. A reasonable correlation between the three is the assumption that the same mechanism is operable in all.

The difference between abortion, prematurity, and stillbirth appears to be mainly one of degree. The villous pathological lesions found in stillbirth more closely resemble those of abortion in the completeness of architectural destruction. In prematurity there is invariably a markedly reduced but continued fetal placental circulation.

The Rose-Waaler titers do not reach the high levels found in prematurity in either stillbirth or spontaneous abortion, and it is our impression that mild proliferative villous lesions are associated with high levels. With more marked collagenization the titer tends to revert toward normal.

It can be argued that the outcome in this particular complication of pregnancy irrespective of whether it is called abortion, prematurity, or stillbirth depends on the intensity of maternal antibody production, concentration of fetal agglutinating substance inhibitor,[5] and the resultant rate of villous collagenization. If during the first trimester there is an outpouring of antibody and a concomitant failure in inhibitor production, villus collagenization will be rapid and abortion will result. On the other hand, irrespective of the height of the antibody level, if the inhibitory substance concentration approximates it, collagenization will be slow and the reduction in villous circulation will move at the same rate. Whether the end result is prematurity or stillbirth will depend on the degree of anoxia to which the fetus is subjected after this disruption in villous vascularity.

If during this more prolonged process there is a sharp rise of antibody over inhibitor, the rate of collagenization should, in theory, respond by acceleration, leading to a rapid ablation of villous circulation with concomitant intrauterine fetal death. The basis for the hypothesis involving an imbalance between agglutinator and inhibitor and a concomitant reaction at tissue level has been given in detail elsewhere.[5]

There are two other facets of interest. First, a large proportion of the mothers in our series of spontaneous abortions, premature births, and stillbirths had a previous history of one or other of these conditions in previous pregnancies. This fact is in favor of the supposition that there is a persistent unstable relationship between mother and fetus. Second, an inspection of the cases in the series shows an erratic scatter of "cord around the neck" and toxemia in relation to stillbirth, suggesting that they may be coincidental but not necessarily the basic causes of fetal death.

Summary

The placental villi and the Rose-Waaler titers of the maternal serum have been examined in 30 cases of stillbirth. Seventeen showed an abnormal Rose-Waaler titer combined with proliferative villous lesions. In 8 the villi were collagenized but the Rose-Waaler reaction was normal. In one the villi appeared normal but the titer was increased.

Spontaneous abortion and prematurity show similar histological and serological patterns. The incidence of these findings in each group is approximately the same.

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Periplacental hemorrhage and renal necrosis in protein and choline deficient pregnant rats following progesterone administration

A preliminary report

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PREVIOUS work from this laboratory had confirmed that a choline deficient diet produces renal cortical necrosis in male and female weanling rats.[5, 6] The young pregnant rat, however, when fed a similar diet, does not develop such renal lesions; she maintains the pregnancy and is delivered normally.[7]

In further experiments, some of which are reported here, the combined effects of hormones and a choline deficient diet were determined. It was found that progesterone administration in such circumstances is followed in a few animals by periplacental hemorrhage, intrauterine death of the fetus, renal cortical necrosis, and liver necrosis. The precise effect of the deficient diets however remains problematical.

This combination of uterine hemorrhage and renal cortical necrosis is reminiscent of the human condition of abruptio placentae. Consequently, the experimental findings are of great interest even though a close comparison between the human and animal lesions is not possible at this early stage.

Materials and methods

Rats of the Wistar albino strain were used throughout. At mating their weights varied between 118 and 160 grams. All pregnant rats used in the experiments were virgin before mating.

Three diets were used: (1) choline deficient[5]; (2) a choline deficient diet with 0.5 Gm. per cent choline chloride (the protein in this diet, as in Diet 1, consists of casein, 15 per cent, gelatin, 6 per cent, and fibrin, 1 per cent; (3) normal rat meal.

The females were placed with stock males for a period of 7 days. During this period and for the whole of the ensuing pregnancy the animals were given one of the three diets. After the mating period the females were housed singly. Nineteen days after the first day of mating the rats were given a total of 20 mg. intramuscular progesterone BP (in ethyl oleate) in four daily doses of 5 mg. each. Twenty-one pregnant females were injected, 7 on each of the three diets. Fourteen nonpregnant female rats were also injected after equivalent periods on the test diets.

It is necessary to stress that no attempt was made in this experiment to determine the exact time of mating. This fact is probably of some importance and will be referred to again later.

Eighteen of the 21 animals were killed within 24 hours of delivery, one following an antepartum hemorrhage and 2 before delivery but after the nineteenth day of gestation. All organs were observed at au-

From The Rotunda Hospital Laboratory.
Aided by a grant from the Medical Research Council of Ireland.

topsy but histological examination was carried out only on the liver, kidney, and the uterus with contents. Routine staining methods were used.

The fetuses which were delivered alive were allowed to survive and were fostered successfully. Histological examinations were not carried out on those fetuses which had died in utero; most were macerated.

The apparent gestation period and the litter numbers did not differ in the three dietary groups.

Results

Uterine. Four animals had an *intrauterine hemorrhage* with death of most or all the fetuses; one had no antenatal disturbance at all but was found to have intrauterine hemorrhage at autopsy and the fetuses were dead. Another had an antepartum hemorrhage 3 days after the last injection and shortly before delivery; later 4 dead and 3 live fetuses were either delivered or found in utero at autopsy. A third had a minor hemorrhage on the third day after injection and thereafter the fetuses resorbed. In none of these animals did necrosis of the liver and kidney occur and the blood urea remained within normal limits.

A fourth animal requires special mention. She had an antepartum hemorrhage 2 days after the last injection of progesterone, became very ill and eventually moribund. She was killed 24 hours after the onset of the hemorrhage at a time when a deadborn fetus had been delivered. At autopsy several dead fetuses were still present and most of these were macerated. The uterus had a characteristic blotchy appearance due to intrauterine hemorrhage. The blood was greatest in amount at the angle between the placenta and the uterine epithelium and surrounded the placenta here like a rim. There was no gross lesion of the metrial gland or of the uterine wall. The trophoblast of the junctional zone was patchily necrotic but the significance of this is doubtful with such limited material, especially since a certain amount of trophoblast necrosis is found in normal animals at term. This animal had a severe renal lesion and this is described in the next section.

Table I. Occurrence of uterine lesions in animals fed different diets

Type of diet and number of animals	*Uterine disturbance*		
	Normal delivery of live fetuses	*Intrauterine death of fetuses*	*Intrauterine hemorrhage and death of fetuses*
Choline deficient, 7	4	Nil	3
Choline deficient plus added choline chloride, 7	5	1	1
Rat meal, 7	7	Nil	Nil

Intrauterine death of fetuses. The fetuses of one animal died without evidence before or at autopsy of intrauterine hemorrhage. On the morning of the fifth day following the last injection she became ill about 12 hours before delivery and delivered overnight of 4 dead fetuses. At autopsy the uterus was completely involuted. No lesions were seen but the blood urea was 144 mg. per cent and the kidney showed severe necrosis histologically.

Table I shows the distribution of the affected animals among the dietary groups.

Somatic lesions. Three animals, one from each of the dietary groups, sustained lesions of the liver or kidney or both.

1. In the choline free group, one animal which had intrauterine hemorrhage and death of fetuses, showed at autopsy extreme pallor of the renal cortex; the blood urea was 177 mg. per cent. There were no other lesions. Histologically the liver showed the usual fatty change due to the choline deficient diet but there were no foci of necrosis. The histological appearance of the kidney may be summarized as a severe confluent focal renal cortical necrosis such as is described in humans,[8] but with, in addition, an almost complete necrosis of the outer half of the medulla. Certain areas of the kidney remain alive—a subcapsular rim of the cortex, the mesial cortex, the tip (inner

half) of the medulla, and small areas surrounding the origin of the intralobular arteries from the arcuate arteries. This distribution of damage is probably related to the blood supply of the kidney and is of considerable interest; it is referred to again later.

2. An animal on a choline deficient diet plus added choline chloride sustained intrauterine death of her litter. Histologically the kidney showed a widespread necrosis of proximal convoluted tubules. There were no hepatic lesions.

3. One animal of those fed on rat meal had a normal delivery of 7 live fetuses a little over 48 hours following the last injection of progesterone. At no time was she ill, nor did she show antepartum hemorrhage, and there was no undue blood loss at delivery. By the next day, however, all the fetuses had been eaten. At autopsy 24 hours after delivery, there was a pleural effusion, renal cortical necrosis, and a small focus of liver necrosis. The blood urea was 202 mg. per cent. There were no other changes. Histologically, the liver necrosis was small and centrolobular. The renal condition was a widespread confluent focal renal cortical necrosis.

All the other animals had no lesions of the liver and kidney and the blood urea values were within normal limits.

Comment

Symeonidis[9] reported that when pregnant rats fed a normal diet (Purina laboratory chow pellets) are injected with progesterone during the last third of gestation 60 per cent aborted or resorbed the fetuses and 40 per cent died or became moribund. At autopsy, periplacental hemorrhage, pleural effusion, eclamptic liver lesions, renal cortical necrosis, and adrenal necrosis were reported. Hester and associates[2] repeated this work but failed to confirm it. They suggested that the discrepancy might be due to the different strains of rats used.

In the present small series, including all dietary groups, adrenal necrosis was not found at all, periplacental hemorrhage occurred in 20 per cent, intrauterine death of the fetus in 24 per cent, and somatic lesions (liver and kidney together) in 14 per cent. This incidence is much less than that in the experiments of Symeonidis.[9] The reason for this difference and for the complete failure of Hester and his associates[2] to produce lesions is not known, but two factors could be important:

A. Diet. In the present series all the animals with uterine lesions had been fed defective diets. As far as somatic lesions are concerned, however, the different diets seemed not to prevent or enhance them—as far as can be judged from such small numbers.

B. The time of gestation at which the progesterone was given. It had been noted by Symeonidis that if progesterone was given prior to the fifteenth day of pregnancy no disturbance followed. It is, of course, well known that hormones may exert different effects depending on the time of gestation at which they are given. In the present experiments no attempt was made to determine the time of mating. Further experiments are therefore being carried out in which progesterone is given at different times of gestation. The possible influence of the different diets could then, in addition, be determined more precisely.

The renal lesions themselves, particularly renal cortical necrosis, seems not to differ from those found in the previous work. The single instance of liver necrosis here, however, was not periportal in site, nor did it resemble the eclamptic liver lesion found in humans.

Probably a point of greater importance is the relationship between the uterine and fetal disturbance and the renal and liver lesions.

From the brief description of the distribution of the renal necrosis and from the anatomy of the blood supply to the rat kidney,[4] it is clear that the etiological factor in the production of the renal lesions is most likely to be vascular, i.e., ischemia, since the areas of the kidney which remain alive are those with a blood supply other

than that via a glomerulus. For example, the tip of the medulla remains alive because it receives a small artery direct from the main renal artery. Arguing from human cases,[8] the most likely site at which ischemia is produced would be at the glomerulus.

It is feasible that the solitary liver lesion and the cause of the periplacental hemorrhage are produced in a similar way, but no evidence can be offered here, particularly in view of the doubtful significance of necrosis of the trophoblast referred to earlier.

One animal in this study sustained a most severe renal lesion although it had a normal delivery. This would suggest that the uterine disturbance does not cause the renal lesions but that both are the result of a common factor, for instance, ischemia. This possibility is of considerable importance for two reasons:

1. If, as already suggested, there is some similarity between this experimental condition and that of human abruptio placentae, then it might be argued that, if the renal and uterine lesions are caused by a single factor in the one, they might be so described in the other. At the present time the renal lesions which follow abruptio placentae are most commonly regarded as being secondary to the uterine catastrophe although the possibility of a single etiological agent has been mentioned.[8]

2. If the renal lesions are vascular in origin and are not secondary to a uterine disturbance, it would appear that progesterone exerts its effects via blood vessels, at least in the particular set of circumstances. Progesterone exerts an effect on the myometrium by a change in the potassium balance of the myometrial cell.[1] It may be conjectured that the effect of progesterone on the renal arterioles is on the smooth muscle of the media with resultant contraction. In discussions of experimental hypertension the possible relationship between the ionic balance of muscle cells of arteries and arteriolar contractility and hypertension has been referred to many times.[8] It is therefore of great interest that Symeonidis[9] reported that hypertension occurred in 5 of his affected rats. He gave no details.

It is obviously necessary to determine the effect of this experimental regime on the blood pressure, and experiments are in progress to provide this and other data.

Summary

When pregnant rats are given parenteral progesterone late in gestation, about one fourth suffer intrauterine death of their fetuses and/or periplacental hemorrhage, and about one sixth have renal or liver necrosis. All the animals with uterine lesions were fed a diet deficient in choline or qualitatively deficient in protein. Nevertheless, until the effect of progesterone at different and precise times of gestation is known, the effect of defective diets must remain problematical.

The similarity of these experimental findings with the condition of human abruptio placentae is pointed out.

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Supine hypotensive syndrome and abruptio placentae

A case report

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IN RECENT years, a clinical phenomenon known as the supine hypotensive syndrome has been described as occurring in 3 to 11 per cent of patients in the third trimester.[1-3] This syndrome is characterized by a significant (30 mm. Hg or more) fall in blood pressure which occurs when the patient assumes the supine position and is suggested as being due to the pressure of a flaccid pregnant uterus on the inferior vena cava, impeding the venous return and thereby reducing the cardiac output.

The case to be described is illustrative of this hypotensive phenomenon and in addition is associated with premature separation of the placenta. At the time of preparation of this paper, there had been only one case reported[4] suggestive of a separation of the placenta consequent to the mechanisms of the supine hypotensive syndrome.

Mrs. R. V. (No. 18230), a 24-year-old Puerto Rican clinic patient, para 1-0-0-1 was admitted to Morrisania City Hospital on Aug. 26, 1959, for an elective repeat cesarean section. The last menstrual period was Nov. 28, 1958, and the expected date of confinement was Sept. 5, 1959. The primary cesarean section was performed in 1957 for a relative cephalopelvic disproportion with delivery of an 8 pound living infant. The prenatal course during the current pregnancy was uneventful with normal weight gain, normal urine, and blood pressures that ranged from 104/80 mm. Hg to 130/85 mm. Hg.

On admittance, physical examination revealed a well-developed and well-nourished white woman, not in labor, at term, and with intact membranes. The vertex was presenting, unengaged, in the left occipitotransverse position. Blood pressure was 130/85 mm. Hg and hemoglobin level 11.5 Gm. per cent.

On the morning of Aug. 28 the patient was prepared on the ward for a repeat cesarean section and was given 25 mg. of promethazine hydrochloride* and atropine, 1/150 grain. She was then strapped on a stretcher in the supine position and sent to the operating suite. Just as she arrived in the operating room, she developed a sudden and severe pain in the back and lower abdomen. Palpation of the uterus revealed it to be somewhat tense and tender. No contractions were felt and the area of the previous uterine scar was not particularly tender. The pulse was almost imperceptible and immediate check of the blood pressure revealed it to be 60/30 mm. Hg. At this point the patient became nauseated, turned over on her side to a semisitting position and began to retch. It was noticed that when the patient assumed this position the pulse became strong and full and the blood pressure rose to 100/60 mm. Hg. Since we did not realize the relationship of the hypotension to the position of the patient, she was placed back to the original supine position in order that an infusion could be started. Once again the patient's pulse became weak and the blood pressure dropped to

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*Phenergan, Wyeth Laboratories, Philadelphia, Pennsylvania.

shock levels. Again she insisted on assuming a less recumbent attitude and again there was a return of a full pulse and normotensive blood pressure. All this time she complained of lower abdominal pain and back pain. No vaginal bleeding occurred. At this time, the diagnosis of supine hypotensive syndrome with partial premature separation of the placenta was made. The patient was transferred to the operating table, and when she was placed on her back in preparation for operation the blood pressure once again dropped to 50/30 mm. Hg.

A low flap cesarean section was performed under local anesthesia. When the uterus was incised, a moderate amount of blood welled up between the uterine wall and the unruptured amnion and was definitely unrelated to the thin margins of the uterine wound. Throughout the operation, the blood pressure remained at shock levels until a living 7 pound, 12 ounce infant was delivered. Immediately thereafter, the blood pressure rose to 150/80 mm. Hg and never dropped below 120/80 mm. Hg again. The patient had received no vasopressors at any time and blood was not given during the hypotensive state.

The placenta was found on the anterior wall of the uterus. At the inferior border, a 3 inch tongue of placenta was found to be separated from the uterine wall.

The postoperative course was uneventful and the patient was discharged on the seventh postoperative day.

Comment

In the case presented, the intimate relationship between the patient's position and the changes in the blood pressure, along with the confirmatory observation that the blood pressure spontaneously returned to normal levels immediately after removal of the baby while the mother was still in the supine position, gives strong clinical support to the hypothesis that the flaccid pregnant uterus may compress the inferior vena cava causing an impairment of the venous return with a consequent drop in blood pressure.

As a corollary to this, the pressure within the inferior vena cava below the level of compression is increased and may reach a degree sufficient to elevate the pressure within the intervillous space and its draining veins to cause a mechanical separation of the placenta.

The intriguing possibility that the increase of venous pressure consequent to the impaired venous return from the uterus may reach a degree sufficient to elevate the pressure within the placental intervillous space and its draining veins to the point of causing a mechanical separation of the placenta was investigated on an experimental level by Howard, Goodson, and Mengert,[1] and Nesbitt and associates.[2] These investigators produced separation of the placenta by ligating the inferior vena cava just distal to the entrance of the renal veins. All work except Mengert's was on experimental animals. Mengert, however, produced abruptio placentae in 2 human subjects by completely occluding the inferior vena cava for 5 minutes while the patient was on the operating table just prior to scheduled cesarean hysterectomy.

Summary

A case history concerning a very dramatic example of the supine hypotensive syndrome associated with mild nontoxic separation of the placenta in a woman not in labor is presented.

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CURRENT OPINION

Clinical conference

"Postpartum psychoses"

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Dr. Dale Boesky. Today we would like to discuss the postpartum psychoses. We are fortunate in having with us Dr. George Morley of the Department of Obstetrics and Gynecology who will comment on the frequent minor emotional reactions to childbirth since our inpatient clinical material is limited to cases of more severe psychopathology. The conference will begin with a brief description of the historical background of the so-called puerperal psychoses, followed by a presentation of statistical data and a brief summary of the descriptive aspects of the syndrome with illustrative cases, and will close with some remarks on etiology and theoretical aspects.

Gregory Zilboorg has made the most notable contributions to the modern literature on postpartum psychoses in a series of papers extending from 1928 to 1957.[7-9] With his characteristic feeling for history, he began one of his earliest papers[9] on this subject as follows:

"The problem of post-partum mental disorders is almost as old as medicine itself. Hippocrates, Celsus, Galen, and Soranus, the most famous obstetrician of antiquity, all observed post-partum psychoses. The very antiquity of the problem perhaps explains the persistence of the tradition which considered the post-partum psychoses to be a specific clinical entity produced by specific causes. Hippocrates considered that the bleeding of a nipple in the post-partum period was an ominous sign pointing to the possible onset of mania; the milk of the woman being suppressed, a mental disorder was in the offing. This view became so firmly entrenched that twenty-three centuries later we find Esquirol earnestly presenting the clinical evidence for and against it. He theorized, also, that the puerperal psychosis was caused by the stoppage of the normal secretion of milk, the latter being directed to the brain instead of the breast. In the century preceding Esquirol, it was believed that deposits of milk formed in the brain after childbirth which either compressed or distended nerve fibers, thus causing a psychosis."

Planchon and Rasher, in the eighteenth century, attributed the puerperal psychoses to the suppression either of the milk secretion or the lochial flow. Early in the nine-

Held at the Neuropsychiatric Institute, The University of Michigan.

teenth century, Levret thought he observed milk particles in the brain of a woman who died during a puerperal psychosis.

Voerhaave insisted in 1700 that puerperal mental disorders were not a clinical entity; in 1745 Berger anticipated the modern view by asserting that childbirth may be followed by various types of psychosis which are no different from psychoses which occur independently of childbirth; in 1850 Merce declared that a multiplicity of etiological factors were involved. Yet, according to Clark, as late as 1900 most texts described mental diseases associated with childbirth as entirely different from other mental diseases. Smalldon[6] remarks that "old names die hard" in recalling that, as late as 1926, Strecker and Ebaugh felt it necessary to remind us that there is no clinical entity covered by the term "puerperal psychosis." In the recent *American Handbook of Psychiatry,* Ebaugh and Tiffany repeat that although it was formerly believed that postpartum psychosis was a specific disease, it is now felt that these are reactive functional psychoses, usually schizophrenia or depression, secondary to the physiologic and psychologic trauma of childbirth, the type of psychosis being dependent upon the premorbid personality.

There is widespread agreement in the literature that postpartum psychoses consist of schizophrenias and depressions. We will consider this controversial question later. We would now like to present 2 typical cases of postpartum schizophrenia. The first will be presented by Dr. Zrull.

Dr. Joel Zrull. Mrs. A. was a 20-year-old white woman who, 8 days after delivery and after her return home, became quite hyperactive and accused her husband and mother of being mentally ill. After admission to the Neuropsychiatric Institute she was noted to talk unceasingly and incoherently. She said such things as, "I saw my father go crazy right in front of my eyes. He wouldn't believe I had a baby." She stated that she was writing a book for her obstetrician, at his request, and the book, in its entirety, consisted of "God is good, life is good, therefore, don't fret." She continued to be very disturbed for many weeks but gradually responded to treatment which included electroconvulsive therapy.

Family and past history revealed an extremely poor relationship with her very domineering mother, who was uncooperative during her stay in the hospital.

In the subsequent years the patient did quite well, although she manifested some psychotic behavior on occasion, particularly with her two subsequent pregnancies.

Dr. Boesky. Dr. Gifford will now present the second case.

Dr. Jeanne Gifford. Mrs. B. was a 22-year-old white housewife, the mother of an 18-month-old boy. Her illness was first noted 2 weeks after his birth when she became obsessed with the fear he would suffocate and had to stay awake and check on his condition all night. She became increasingly nervous and anorexic, and then began to have a regular morning emesis. Four months after the onset of her illness, following an argument with her husband, she "put little Johnnie to bed too hard," and when she herself then jumped onto her own bed she felt her stomach "break." She complained of epigastric pain, became withdrawn and unable to care for her family and home, and was admitted to the Neuropsychiatric Institute 7 months after delivery. She was tired-looking, disheveled, and frightened that she "had no stomach and would therefore die."

She was treated supportively, given Stelazine, and discharged after 3 months, but with only minimal improvement. When followed as an outpatient, her affect continued to be flat; she remained quite uncommunicative, speaking in monosyllables and only in response to direct questions.

A year later, during the first trimester of her second pregnancy, she came in talking loudly, angrily, and inappropriately about her lack of weight gain. She stated she couldn't be pregnant because she had no stomach, and that she feared all her relatives would die. She was readmitted to NPI, a terrified, disheveled girl who complained bitterly about her rotting, ruptured stomach and our failure to recognize her need for a

reparative operation. With supportive treatment and tranquilizers, her anxiety and agitation rapidly disappeared, and she was able to return home a month after admission. However, she remained silent, flat, and withdrawn. Six months later her second boy was born; there was no return of the more incapacitating symptoms at this time.

Dr. Boesky. Now for the statistical aspects of postpartum psychoses. The first question to be considered is the proportion of postpartum psychoses to all other cases of psychosis in mental hospitals. In 1847, MacDonald reported puerperal reactions in 7.1 per cent of all female patients admitted to Bloomingdale Hospital. The past 110 years have borne this out. The range of incidence reported by 8 investigators in the last 50 years is from 3 to 18 per cent, but most agree that these cases constitute about 7 per cent of all female patients admitted to mental hospitals.

The next question is how many cases of postpartum psychosis occur in the pregnancies of a given number of normal women. This has been variously estimated from 1 in 400 confinements to 1 in 1,400. The incidence is probably higher than the usually quoted 1 in 1,000 cases, since it is widely recognized that many psychotic patients, for a wide variety of reasons, never reach psychiatric attention.

We turn now to the more difficult question of the breakdown of these cases by diagnosis. The majority of authors report roughly 50 per cent schizophrenias and 50 per cent manic-depressive psychoses, and agree that only 2 to 4 per cent are toxic-infectious psychoses. One can see, however, that uniform diagnostic criteria have not been applied over the years. Many of the cases labeled depression, particularly 20 to 50 years ago, apparently included patients who presented inappropriateness, hallucinations, and delusions typical of schizophrenia. The same would hold for the diagnosis of "delirium without toxic factors" which was used at the turn of the century. In 1929 Zilboorg[9] stated that schizophrenia accounted for rather more than 50 per cent of the postpartum psychoses, and most other workers agree with this figure. It is also generally agreed that of the Kraepelinian subtypes, catatonic reactions are the most frequently observed.

Smalldon[6] confirms the general impression that true toxic postpartum psychoses have been very infrequent in recent years, reporting only 3 to 6 per cent of these in his series of 220 patients with postpartum psychoses.

I would like to turn now to an interesting, if puzzling, statistical question. I am referring to the relationship of postpartum psychoses to pregnancy order; in other words, whether the psychosis usually occurs after the first pregnancy, the second pregnancy, and so forth. My own impression had been that this was more likely to occur in the primiparous woman, but, as we shall hear, this is apparently not the case.

Zilboorg[9] asserts that more than 50 per cent of postpartum psychoses occur in multiparous women. Smalldon reports that 55 per cent of his cases were in primiparas and that of the 45 per cent that were in multiparas, roughly half occurred after the second delivery and a quarter after the third. Brew and Seidenberg[2] also reported that only 50 per cent of their cases were in primiparas, but they stated that at least a quarter of their multiparous patients with psychoses had moderate to severe emotional episodes during previous pregnancies. They are the only authors to comment on this important aspect.

In trying to account for this phenomenon, Zilboorg[9] stated: "Characteristically the women who develop post-partum schizophrenia or any other post-partum psychosis tend to be multiparae; there appears to be a latency period between the pregnancy which is undergone with impunity and the pregnancy which finally results in a psychosis; this period is usually from 3 to 10 years but is marked by gradual withdrawal from domestic interests."

Helene Deutsch[4] also attempted an explanation: "It is particularly interesting that so many patients develop a psychosis not after giving birth to the first child, but only

several years later, after having another child. I have found that the pathological reaction of emotionally deranged, schizoid (but not psychotic) women are very often postponed and centered on later-born children. It seems that, in these women, the psychic balance is harder to preserve when the maternal relationship must be spread to several children than when it is concentrated on one child."

This is, perhaps, more a restatement of the problem in other terms than an explanation. Even if we accept the concept of a latency period, we are, perhaps, faced with an artifact which has given rise to a pseudo-problem. I refer to the fact that a close reading of many of these reports suggests that the data were gathered primarily by reviewing old charts, and the possibility arises that careful histories were not always taken originally. Thus, the occurrence of a psychotic episode in the first pregnancy may very well have gone undiscovered when the patient was anxious to pass over this. We must also keep this in mind in evaluating the next category, the time of onset of the psychotic episode.

Zilboorg confirms the long-held view that the puerperium is the most frequent phase in which psychosis occurs. Various authors have estimated that 3 to 23 per cent of psychoses occur in pregnancy, 6 to 45 per cent occur during lactation, but 40 to 86 per cent occur during the puerperium. A variety of statistics could be quoted, but I can say in summary that there is general agreement that far and away the most frequent time of onset of the psychosis is in the several weeks following delivery rather than during the pregnancy. One does not know, however, whether this impression is based on anamnestic data or on clinical observations or on a mixture of both. This is further complicated by the assertion of Brew and Seidenberg that the time of onset is linked to diagnosis. They report that careful histories taken in their cases of *depression* reveal the time of onset to have been predominantly during pregnancy rather than after delivery, and that it was often traceable to the first trimester. Strecker and Ebaugh also report premonitory signs in 50 per cent of their manic-depressive patients and in 35 per cent of their schizophrenic patients. However, these studies are so heterogeneous that we cannot validly compare one study with another.

We can now direct our attention to some of the simpler statistics. The average age of the patients at the time of onset is 28.5 years, according to Zilboorg.[9] This is confirmed by Brew and Seidenberg.[2] The latter were the only authors who studied the sex of the newborn child in their psychotic patients, and they reported no correlation with psychosis; 52 per cent of their 103 patients were delivered of boys, and 48 per cent had girls. As for the ratio of illegitimate pregnancies to postpartum psychosis, they report that 10 per cent of their cases were in patients with illegitimate pregnancies. In this connection, Kasanin once claimed that if the outbreak of psychosis is to occur during pregnancy, it is much more likely to appear during a pregnancy which is illegitimate.

It is interesting to find that these cases are not characterized by obstetrical complications during pregnancy and delivery. Brew and Seidenberg[2] report that in their series of 103 cases, there were only 2 cases of toxemia, 2 prolonged labors, one set of twins, one stillbirth, no disproportionate number of abnormal positions, and no cesarean sections. There was only one cesarean section in Combs'[3] series of 50 cases. He also reported a 14 per cent incidence of repeated postpartum psychotic attacks and stated that these were just as frequent in women with 3 children as in those with 6, 7, or 8.

Figures on prognosis vary considerably. Brew and Seidenberg state that 20 per cent of their schizophrenic patients and 50 per cent of the manic-depressive patients were discharged in 4 months. Long-term follow-up of their remaining patients revealed that only 50 per cent of their schizophrenic patients were released from state hospitals after an average stay of 2.1 years, compared to an average stay of one year for comparable female schizophrenic patients in the same hospitals whose psychoses were not related to childbirth. Seventy-five per cent of the manic-

depressive patients were released after an average stay of one year. Zilboorg[9] states that his review of his own patients as well as that of other workers reveals that anywhere from 25 to 50 per cent fail to recover. On the other hand, Smalldon[6] and Strecker feel that about half of these cases are characterized by a tendency toward rather rapid remission.

Turning now to clinical material, we would like to present 2 cases of postpartum psychosis in which depression was the important feature. The first case will be presented by Dr. Allis.

Dr. Lyle Allis. Mrs. C. was a 23-year-old woman who was admitted to the Neuropsychiatric Institute complaining of anxiety, depression, insomnia, and nausea. The symptoms began 3 months prior to admission, one week after the birth of her second child, a girl. She also had a boy 3 years old. She stated that she had been mildly depressed after his birth.

This patient had always been a meticulous housekeeper and after the birth of her second child she became increasingly upset because she could not maintain her high standards of cleanliness. She became frightened when holding the child and felt she could not take care of it and that she was not a good mother. She became tense, anxious, and was troubled with insomnia, nausea, and vomiting. She was very depressed and felt incapable of doing anything about the house. She responded well to supportive treatment and was discharged 6 weeks later; she continued to do well thereafter.

Dr. Boesky. Dr. Woollams will present the next case.

Dr. Stanley Woollams. Mrs. D. was a 28-year-old housewife who was admitted complaining of depression, anxiety, nausea and vomiting, and feelings of rejection toward her first child.

All her life, the patient had felt lonely and without friends and had probably never had any close interpersonal relationships. She said her parents were about 40 when she was born and she had never felt close to them or to anyone else. She had several affairs during her marriage.

Her symptoms began 2 weeks after the birth of her child, and she was admitted to the hospital 5 months later. She had a normal pregnancy and delivery and did well during the postpartum period, until her mother, who had been helping her, left the home. The patient became overwhelmed with feelings of inadequacy, felt very depressed, cried a great deal, and could hardly retain any food. After 3 weeks of treatment as an inpatient, the depression lifted; however, her lack of feelings toward her child continued.

Dr. Boesky. The statement that occurs in the literature that postpartum psychoses are either schizophrenias or depressions seems oversimplified. It is common experience to see borderline and severly neurotic syndromes characterized by obsessive hatred for the newborn child, in which the mother is incapacitated by the need to lock up knives, to avoid stores selling sharp objects, to get up every hour during the night to check the child's breathing, and so forth. Further on in this spectrum of psychopathologic reactions to childbirth would lie the minor depressions and "fifth-day blues" about which Dr. Morley will comment.

For this reason, it would be unfruitful to pursue the question of etiology at length, other than to note that modern aseptic techniques have reduced the true toxic-infectious postpartum psychoses to a very small number. The problem of etiology of these conditions is, therefore, the problem of etiology of all psychopathology.

We can turn now to the theoretical aspects of the subject. Zilboorg[7] has written so extensively on this subject that it is difficult to summarize his ideas without being misleading. In general, in his earlier writings he was impressed with the general emotional immaturity of the patients suffering from postpartum psychosis. He tried to find certain personality characteristics which would enable him to predict which of a number of women would become psychotic after delivery, but found he was unable to do this. In his later years, he felt that a much more important predictive factor was a severe

unconscious hostility for the child. Of greatest practical importance is his warning that suicide and infanticide must be considered potential risks in these cases. That is one point on which there is general agreement.

Most authors also agree that severe unconscious antagonism toward the child is an important element in the psychopathology of these conditions. Smalldon[6] describes the behavior of his manic-depressive patients in these terms: "Some talked of hating the baby, of disliking it for destroying their figures or for taking too much of their time; some openly wished they had not given birth to the child or said they wanted one of the opposite sex; others insisted that the baby belonged to someone else, some feared that harm would come to the child or that they would injure it. Others threatened to kill the child and made a number of infanticidal attempts. There were mothers deliberately sticking pins in their babies, attempting to throw them from windows, attempting to choke and drown them, refusing to nurse the child and deserting the child. In half the cases, hostility was manifested by indifference to the child. Twenty women clung to the delusion that their child was dead. This was far less common in the true toxic-infectious group." Many other authors confirm these observations and report that denial of the marriage and avoidance of the husband or severe antagonism toward him are quite frequent.

Brew agrees with Zilboorg's impression of the frequency of latent homosexuality, which can be inferred from the great frequency of paranoid delusions with the content of homosexual accusation. The delusional accuser is frequently the nurse who is described as wearing perfume to get the patient sexually excited, stopping up the patient's bowels, making the patient do things against her will, calling the patient a queer, spoiling her blood, and so forth. However, it remains an open question whether this occurs more frequently in these cases than in other cases of schizophrenia.

It was asserted 120 years ago by Conolly, and long believed true by others, that periods of national emergency which were alleged to exert an influence on all forms of insanity also increased the incidence of puerperal psychosis. However, Brew and Seidenberg followed their patients through the economic depression of the 1930's and through World War II and careful statistical analysis disproved this old impression.

Brew, in attempting to predict which patients would develop postpartum depressions, states that their premorbid personality is characterized by pronounced narcissism and a pathologically dependent relationship to the mother. Helene Deutsch[4] has this to say about this type of woman: "Certain infantile women do not achieve the expected development toward reality, they do not renounce the fantasy relationship with the child, and they play at motherhood like little girls. They are very proud of their children, have a triumphant feeling with regard to their own mothers, are overjoyed by the gifts they receive and are eager to show off their child. When the game becomes serious and the infant begins to make demands the mother is seized by the fear of having her freedom restricted, of being dependent upon the child, and of impoverishing her own ego, which, being still in need of development, is in real danger."

In a discussion of psychopathology, it is easy to lose sight of this pertinent observation by Deutsch: "It is noteworthy that childbirth sometimes has a pathogenic but at other times a therapeutic effect. For instance, in some cases obsessional neurotic states become much milder after delivery, in others they become acute; depressions are moderated or are intensified to psychotic proportions."

In another context, Deutsch states that the strength of the woman's identification with her own mother is a crucial factor in determining the course of pregnancy. The capacity for motherhood is related to this identification. The pregnant woman must find a harmonious compromise between her deeply unconscious identification with her child and her identification with her own mother. Whenever one of these identifica-

tions is rejected, difficulties arise. We will now present 2 cases which illustrate many of these points and which are of particular interest because of the actual death of the child in the first case and the severe deformity of the child in the second case. Dr. Murphy will present the first case.

Dr. Thomas Murphy. Mrs. E. was a 24-year-old housewife who was admitted to the Neuropsychiatric Institute because of confusion and inability to care for her children at home. At the time of admission she was obviously schizophrenic, with a markedly flattened affect and a gross thinking disturbance.

The patient's history revealed a traumatic childhood with a separation from the parental home at the age of 5. She left her foster home at the age of 12 and lived with an older sister. She married at 15 when she became pregnant.

Her first and second pregnancies, deliveries, and postpartum periods were unremarkable. During this time she functioned fairly well, in spite of a great deal of marital discord. After 6 months of her third pregnancy, she was delivered of a 3 pound premature baby boy. The patient did well after the delivery and went home 7 days later, leaving the infant in the hospital. Within a week she became depressed and entered into a psychotic depression for 3 months. During this time she was withdrawn, lay in her bed most of the time, and would hide in the closet and not recognize her husband and children. She was not hospitalized because of her family's objection to this.

After a spontaneous recovery, she began caring for the baby when he was 5 months old. She worried a great deal about his health even though he appeared entirely healthy at this time. When the baby was 8 months old, and in the care of a babysitter, he fell from the couch and struck his head, leaving a mark on one temple. Although the baby appeared well after this, 2 days later he had a convulsion and died of a brain hemorrhage. The patient's immediate reaction to this was to think that her husband had struck the baby, causing his death. She left her husband and returned to her family for 6 months.

Four times in the last 5 years, just at the anniversary of the baby's death, the patient has had psychotic episodes and has had to be hospitalized. Apparently she has functioned fairly well between these episodes. In addition to her feeling that her husband had killed the child, she also admitted to great feelings of guilt about being absent when the child was hurt and also about his premature birth.

Dr. Boesky. Dr. Garlock will present our last case.

Dr. Grant Garlock. Mrs. F., a 26-year-old white housewife, was originally admitted to the University Hospital with her 1-week-old infant, who was noted to have microcephalus and webbed fingers and toes.

The patient had become more and more disturbed during the year prior to admission. She spoke of witches casting spells on her and felt that television shows contained personal references to her.

After transfer to the Neuropsychiatric Institute, she remained almost mute at first, but exhibited a constant sardonic smile. Later she spoke at length of a delusion that she had been physically and sexually assaulted by numerous men while her husband sat idly by and allowed this to occur. Later still, she revealed a new delusion, feeling that, after the assaults, she had had about 30 babies in the last 6 months. Of these, she claimed 3 were born with developmental anomalies.

Dr. Boesky. It would be pertinent to ask how we can fully understand the mechanisms of postpartum psychopathology except from the vantage point of our knowledge of the feelings experienced in normal pregnancy. This is something about which we know very little. The subject is discussed with unusual clarity by Grete Bibring[1] in her recently published article entitled "Psychological Processes in Pregnancy." She and her co-workers were perplexed by the unexpected but frequent observation that a disproportionate number of pregnant women demonstrated quite severe psychopathology.

In their interviews with mothers who seemed superficially "normal," there was a very high incidence of magical thinking, depressive reactions, primitive anxieties, paranoid mechanisms, and borderline states. Of further note, the histories rarely revealed major pathology prior to pregnancy. Last, and most striking, was the ease with which therapeutic results could be obtained. One would have predicted, on the basis of the severe pathology so obviously seen in pregnancy, that dire sequelae were in store after delivery. This was not necessarily so. The frequency of these observations, when compared with the average hospital population, finally suggested to Bibring that this picture may pertain to the condition of pregnancy in general rather than to the specific problems of the individual. Bibring extends this idea and compares pregnancy to puberty and menopause. It, also, is a stage of crisis normally, with relative ego weakening characterized by new and increased tasks of adaptation, the revival of unsettled conflicts and the loosening of partial, inadequate solutions of the past. It is, therefore, a fallacy to assume that only women who are in some way neurotic will be adversely affected by their pregnancies, just as it would be fallacious to assume that only the neurotic child will be troubled by adolescence or the neurotic woman by menopause. Therefore, at our present state of knowledge, we cannot accurately predict who will or will not suffer from postpartum psychoses.

Dr. Morley: Relative to the question of the incidence of primiparous to multiparous women who developed postpartum psychotic reactions, I think an important point related to statistics must be kept in mind. A woman is a primipara only once, whereas she is considered a multipara with every subsequent pregnancy. In order, therefore, to obtain a more accurate incidence one must carefully compare the number of times psychosis occurs in women with the first child to the number of times it occurs with the second child, the third, etc. This may have direct bearing on the apparent paradox to which Dr. Boesky referred, since statistical weighing would support the idea that psychoses actually are far more frequent in primiparous women than the data would suggest at first glance. In regard to incidence, itself, I would suspect it to be greater than most people realize since the condition may be unrecognized or overlooked by the attending obstetrician.

Now I would like to comment about the so-called "fifth-day blues," which is not an infrequent finding on the postpartum ward. The physiologic and anatomic process of the pregnancy, the labor, and the postpartum period are basically similar in all patients with comparatively few variations. The problem arises, however, because the "personality" differs so frequently. It is this deviation or departure from the norm that gives rise to this clinical entity. The patient will frequently say that she does not know why she feels this way, that it is perfectly silly of her to carry on like this, but she just cannot help herself. The patient cries as a result of her emotional state, yet laughs through her tears. The treatment of this condition varies somewhat, but usually is confined to "having a good cry," "getting it off her chest," or "talking it out."

The probable mechanism involved is quite interesting. Throughout the pregnancy the patient is receiving increased attention from her husband, her relatives, her friends, and her obstetrician. This attention increases during the pregnancy and labor. It reaches its peak approximately 2 to 3 days after the delivery, during which time there has been considerable medical and nursing attention, and the patient has received many visitors, telegrams, flowers, and cards. As the attention titer drops off—of necessity—the responsibility titer of the patient to her baby and to herself begins to rise and increases steadily. Up to now the baby has been cared for almost exclusively by the nursing staff. If we are going to see this transient and mild reactive depression develop it usually occurs when the level of these two titers crosses, thus precipitating this effect. This entity is clinically apparent in approximately 10 per cent of the postpartum pa-

tients. Frequently, there is a recrudesence of this condition to a lesser degree after the patient is discharged from the hospital, for similar reasons.

Dr. Andrew Watson. I think that Dr. Theresa Benedek's concept of parenthood as a stage in personality development is quite important from the point of view of planning therapy for these mothers. Many mothers want to care for their child but don't feel they are capable of it. Then they tend to regress. If the regression is encouraged or even passively permitted, the mother rapidly gets worse; if it is blocked and if the mother is helped in psychotherapy to take on the responsibilities of parenthood, then she can attain normality. It is quite important that psychotherapy should be started early or the mother can rapidly deteriorate to psychosis.

Dr. Herbert Schmale. I would like to comment on another aspect of regression in these mothers. The mother who has an unstable personality herself is particularly threatened by her infant who, by his very nature, presents the acme of regression and helplessness. A mother of this type sees in her child the very state that she fears she may fall into herself. Her hatred of the child is a fear that she herself might fall apart.

Dr. Morley. In closing, I would like to present a question to our psychiatric colleagues. Is this truly a postpartum psychosis or is the pregnancy just one of many stress situations which could cause an overt psychotic episode?

Dr. Thomas N. Cross. Perhaps I could reply to Dr. Morley's question. The answer to the first part is "no." The postpartum psychoses differ in no way from other psychoses, and to use the term is as meaningless as saying "postpartum headaches" or "postpartum arthritis." However, let us look carefully at the last half of his question—"is pregnancy just one of many stresses which could precipitate a psychotic episode?" The answer to this would also have to be "no," for the two halves of Dr. Morley's question are really not quite the same. There is nothing unique about, say, postpartum schizophrenia; it is the same as schizophrenia seen under other circumstances; but any psychotic episode results from a highly specific imbalance in a patient's adaptive capacities, and pregnancy, or anything else, would therefore *not* be "just one of many stresses that could precipitate psychosis." Nothing ever is. Incidents that trigger a psychotic break in one patient mean little to another; it requires a specific combination of stresses on one hand and weaknesses on the other to result in psychosis. Though this may seem a little like hairsplitting, it is an important point.

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Reviews | Abstracts

Edited by
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Reviews of new books

Heredity Counseling. Edited by Helen G. Hammons. 112 pages, 1 figure, 4 tables. New York, 1959, Paul B. Hoeber, Inc. $4.00.

It can hardly be doubted today that the young science of genetics is rapidly reaching maturity, nor can the importance of its contributions and its potential to the solution of difficult medical problems be denied any longer. In this rather small book based on a symposium sponsored by the American Eugenics Society in 1958, genetic counseling, as one aspect of the relationship of genetics to medicine, is discussed by 17 well-known leaders in the field.

The content is divided into two parts. Part I—Genetics in Medical Practice—is concerned with the need for genetic counseling in pediatrics, dentistry, and Public Health nursing. Part II—Heredity Counseling—discusses the structure of heredity counseling services, referral procedures, types of advice given by heredity counselors and the dangers of inadequate counseling.

It is regrettable that the discussions do not go far enough to satisfy more completely the desire for a long sought after and much needed guide to this increasingly important subject. Quite properly, counseling by those not trained in genetics is discouraged, but despite these admonitions it would appear that a more detailed discussion of vital problems encountered and the advice given in specific instances drawn from the undoubtedly vast experiences of this elite group of authors would have enhanced the value of the book. For its size, nonetheless, it does contain much useful and timely information, especially for those not genetically trained and who are interested in becoming acquainted with the problem of heredity counseling as it is today.

Therapeutic Radiology. By William Moss. 403 pages, 146 illustrations. St. Louis, 1959, The C. V. Mosby Company. $12.50.

Dr. Moss has described the contents of his book in its preface. It is not a recipe for radiotherapy nor is it an encyclopedia. But it is an introduction to selected clinical problems in therapeutic radiology, and it expresses a philosophy of radiotherapy intended to improve patient care.

The introductory chapter stresses the clinical nature of radiotherapy, wherein the patient and his disease comprise the ultimate reality. To cope with this reality the therapist combines his clinical experience with the disciplines of radiation physics, surgical pathology, and radiobiology. Each patient must be treated with an individualized technique and dosage, but general treatment policy is based on the end results that have been reported from major cancer treatment centers.

The remaining chapters discuss the tumors of the various major anatomic regions of the body. The natural history of the tumor and the effects of radiation on the normal tissues of each region are described. End results of various modalities of treatment are tabulated. The author then proposes treatment policy and technique based on the rational evaluation of these factors of tumor history, radiation tolerance of normal tissues, and end results.

Dr. Moss is a therapeutic radiologist and Assistant Professor of Radiology at Northwestern University School of Medicine. His text is intended for the student of radiotherapy. Its brevity, emphasis on major issues, excellent bibliography, illustrations, and tables are all assets. A general discussion of clinical staging and methods of presentation of end results would be useful additions to the book.

Fermente—Hormone—Vitamine, Vol. 2, Hormone. By R. Ammon and W. Dirscherl. Third edition. 897 pages, 144 figures, 88 tables. New York, 1960, Intercontinental Medical Book Corp. $35.25.

The tremendous accumulation of facts in the field of hormones has made necessary an entire volume devoted to a subject which in 1948 filled only the middle part of the second edition of *Fermente—Hormone—Vitamine*. Written by two experts in biochemistry, in collaboration with authors contributing chapters on zoology and botany, this book concerns itself with a description and discussion of the chemistry of hormones, their physiology, and their role in mammals, vertebrates, invertebrates, insects, and plants. This is truly an interdisciplinary endeavor, an excellent guide in the biochemistry of hormones and related problems, pointing out the significance of hormones with reference to enzymes and vitamins. A clear and concise style and an emphasis on chemistry contribute to a more fundamental understanding of the new research problems.

The obstetrician and gynecologist now has the benefit of an up-to-date book for reference and a systemic presentation, authoritative and critical, of the most advanced knowledge in the field. He should not, however, expect to find a clinical endocrinology, although clinical problems are dealt with briefly.

Of special interest are chapters on sex hormones, the relationship between female and male hormones, and the influence of the sex hormones on the embryo.

An index of authors at the end of each chapter and one of subjects at the end of the book add to the practical value of this basic work, for which the authors as well as the publisher are to be highly commended.

Trends in Genetic Analysis. By G. Pontecorvo. 145 pages, 18 tables. New York, 1958, Columbia University Press. No. XVIII of the Columbia Biological Series. Price $4.

The concept of the gene as a simple entity with the simultaneous properties of indivisibility in heredity, specificity of function, and ability to mutate is no longer satisfactory as a working model for an understanding of the fine structure of the genetic material. Above all other recently developed techniques, those of microbial genetics have enormously increased what the author refers to as the "resolving power of genetic analysis." The essential process on which genetic analysis is based is recombination, i.e., the apparent exchange of genetic material (information) between chromosomes. Hence, the discussion is centered about this powerful but little understood genetic tool and its use in one of the most exciting developments in genetics, the splitting of the functional unit of inheritance, previously called a gene, into subunits. By recombination, these subunits can be distinguished within the functional organized structure now referred to as the cistron. References are made to various works with microorganisms and fungi, particularly neurospora and aspergillus, to illustrate the text.

The six chapters that make up the book are entitled: I. Genetic Analysis and Its Resolving Power, II. Allelism, III. Structure and Function of the Genetic Material, IV. Recombination, V. Mapping Chromosomes via Mitotic Recombination, and VI. Novel Genetic Systems. Based on a series of lectures delivered by Professor Pontecorvo to the Department of Zoology of Columbia University in 1956, the scope of which was a reappraisal of the theory of the gene in the light of the present knowledge, the text is concerned with only those avenues of development in genetics with which the author is most conversant from firsthand experience.

Quite clearly, the book is intended for the geneticist and hence may at times be difficult for the novice since a more than cursory knowledge of the subject by the reader is assumed. For the geneticist and those in related fields familiar with classical genetics the book offers a concise and clearly written discussion of the present concept of the gene as developed from the work of Benzer, Watson and Crick, Levinthal, Plaut and Mazia, Kacser, Pritchard, and others, including those of the author.

Clinical Endocrinology. Edited by Edwin B. Astwood. First edition. 724 pages, illustrated. New York, 1960, Grune & Stratton, Inc. $18.75.

This 724 page book is edited by one of the foremost endocrinologists of this country. He has gathered together 82 contributors most of whom are well known in their various fields.

As its title would indicate, it is primarily devoted to the clinical aspects of the subject although by necessity the research and laboratory components are discussed in many areas.

Each topic is presented in a concise manner with only the most important points discussed. This is conducive to short chapters that are readable and the material easy to digest without getting lost in a mass of words. As far as possible only material that is fairly well accepted is given. The lack of the theoretical makes the book practical for the clinician.

Considerable space is devoted to the abnormalities of sex and thus emphasizes the progress that has been made in recent years in knowledge of these problems.

The last section of the book is devoted to hormone assays and special tests. This is a valuable portion for it brings together in one place the various tests for all the hormones and should prove to be a valuable reference.

The reviewer enjoyed the book and found it not only informative, but easy reading. It can be recommended for all interested in endocrinology.

Lehrbuch der Gynäkologie. By Heinrich Martius. Sixth edition. 447 pages, 476 figures. New York, 1960, Intercontinental Medical Book Corp. $12.85.

Heinrich Martius is no stranger to the international community of authors and teachers in gynecology, and his works excel in substance and clarity. This sixth edition, bringing up to date his textbook, originally published in 1946, is no exception. Intended for the German student of gynecology as well as for the practicing gynecologist, it presents 12 chapters in pleasant style. In general, the present status of gynecological knowledge and practice in Germany appears to be on a level with that in this country, but a few differences deserve mention.

It was surprising, for example, to learn that in cases of difficult dilatation, laminaria is still being used in Germany, while that instrument is taboo in the United States. Rubin's insufflation test, an office procedure here, is recommended for hospital treatment only; colposcopy, however, is advocated as a *must* in office gynecology. Surprising also was a report that treatment of sterility by artificial insemination *ab alieno* was rejected by the Sixty-second Convention of the German Medical Society in 1955.

For cancer of the cervix the gynecological department of the Woman's Hospital in Göttingen, under the author's directorship, has developed intravaginal radiation of the parametrium by means of a special tube. No reference is made to the selection of cases for operative and nonoperative treatment on the basis of SR and RR cytotechnique of Graham and Graham.

In patients with severe amenorrhea, when the functioning endometrium no longer exists because of inflammation, chemical cauterization, or too vigorous curettage, Martius transplants endometrium.

Also of interest are observations concerning so-called "grippe salpingitis," after which the salpinx frequently heals without defect, regaining its patency, and hypoplasia of the uterus due to mental and physical strain during war.

The chapter on gynecological urology calls attention to the pedunculated muscle fat transplantation from the musculus bulbocavernosus for support after urethroplastic.

A presentation of hormone therapy based on the most recent research in the field makes this text worthy of a place on every gynecologist's shelf.

Atlas der gynäkologischen Operationen. By O. Käser and A. Iklé. 451 pages, 720 figures. Stuttgart, 1960, Georg Thieme Verlag. $35.25.

This splendid atlas, in the opinion of the reviewer, is the equal, if not the superior, of any recent gynecological surgical atlas.

In general it follows the form of similar atlases, with illustrations and division into the appropriate sections. It has an excellent section on minor operative procedures, particularly ring biopsy. It shows marsupialization of the Bartholin gland, a relatively new procedure. It has, in addition to the usual standard operations in the gynecological field, a section on urological and proctological procedures and radical and ultraradical procedures for carcinoma, as well as intestinal operations.

In general this is a most complete and beautifully illustrated atlas, which the reviewer believes is the finest he has ever seen.

High Blood Pressure and Pregnancy. Lance Townsend. 115 pages, 22 figures, 26 tables. New York, 1960, Cambridge University Press. $8.50.

This thesis, submitted for a doctorate in medicine, is a detailed analysis of the pregnancies of 109 hypertensive women seen in 1956, which is compared with an analysis of the pregnancies of 111 hypertensive women seen in the same clinic in 1946 and 1947. In the 1956 series, all patients

were found to have systolic blood pressures of 140 mm. Hg or higher and diastolic pressures of 90 or higher prior to the twelfth week of gestation. In the 1946-1947 series, such blood pressures were recorded before the twentieth week; patients with recognized glomerulo- or pyelonephritis were excluded.

The 1956 patients were followed more closely in the prepartal clinic, their weight gains were more rigidly controlled, salt intake was restricted "when necessary," hypotensive drugs were used "when necessary," and admittances to the hospital for treatment were more frequent and prolonged than in the 1946-1947 cases. "The 1956 regime has significantly reduced the perinatal mortality. . . . " The author attributes this to the improved prepartal care and perhaps gives undue credit to the control of blood pressure by hypotensive drugs. The results, so far as the fetus is concerned, may be summarized as follows:

Group	*Cases*	*Therapeutic abortions*	*Perinatal deaths*	*Fetal salvage*
1946-1947	111	19	10	74%
1956	109	8	8	85%

It would appear that the improved fetal salvage depends upon the reduction in therapeutic abortions, for on the basis of pregnancies allowed to continue the perinatal mortality is not significantly different in the two series ($X^2 = 0.5$; data not corrected for fetal anomalies).

In general, the factors found to influence the fetal prognosis are those described by previous authors: the fetal wastage increased with (a) higher initial blood pressures, (b) rise in blood pressure with the appearance of proteinuria in late pregnancy, (c) the appearance of proteinuria regardless of blood pressure, and (d) smaller fetal weight at delivery. One third of the patients of the 1946-1947 series had spontaneous drops in blood pressure in midpregnancy, and this was a favorable sign for fetal prognosis.

The first 25 pages of the book are given to a good review of the literature.

Significant Trends in Medical Research. Ciba Foundation Series 50, edited by G. E. W. Wolstenholme, C. M. O'Connor, and M. O'Connor. 356 pages, 41 illustrations. Boston, 1959, Little, Brown & Company. $9.50.

This symposium of advances in medical research commemorates the tenth anniversary of the Ciba Foundation. Its 14 papers, in dealing with many of the significant research developments in medicine of the past decade, run the gamut from a discussion on molecular structure by Linus Pauling to Dickinson Richards' studies on pulmonary disease and metabolic problems involving the pancreas as elucidated by Charles H. Best. Included among the eminent contributors to the program are 7 Nobel laureates. Each paper is followed by a stimulating and provocative discussion among the participants. One of the high lights of the symposium is F. G. Young's discussion of the structure and mechanism of action of hormones, which suggests hormonal regulation of the rates at which metabolites pass through permeability barriers. Sir George Pickering raises doubts on our customary classification of hypertension in his extensive treatise on the quantitative approach to disease. Specific protein and amino acid deficiencies in kwashiorkor are elucidated by J. F. Brock by way of intensive dietary variations in afflicted individuals. In spite of the amplitude of the symposium, each subject evolves quite naturally from its predecessor as logically as disease itself can be traced back to enzymatic, molecular, and genetic aberrations.

Books received for review

Clinical Obstetrics and Gynecology, Vol. 3, No. 2, Physiology of Pregnancy. Edited by Ernest W. Page. **Endometriosis.** Edited by Charles S. Stevenson. 536 pages, illustrated. New York, 1960, Paul B. Hoeber, Inc. $18 per year.

Demonstrations of Physical Signs in Clinical Surgery. By Hamilton Bailey. 928 pages, 1142 figures. Baltimore, 1960, Williams & Wilkins Company. $14.50.

Genitale Chylusfistel und Chyluszyste. By Helmut Pabst. 84 pages, 24 figures. Berlin, 1960, Walter de Gruyter & Co. DM 18.

Gynecological Urology. Edited by Abdel Fattah Youssef. 893 pages, illustrated. Springfield, Ill., 1960, Charles C Thomas, Publisher.

The Seven Ages of Woman. By Elizabeth Parker. 609 pages, not illustrated. Baltimore, 1960, Johns Hopkins Press. $6.50.

1959-1960 Year Book of Cancer. Edited by R. L. Clark, Jr., and R. W. Cumley. 533 pages, 172 figures. Chicago, 1960, Year Book Publishers, Inc. $8.50.

Selected abstracts

Acta obstetrica et gynecologica scandinavica

Vol. 39, Supplement 1, 1959.

*Krokfors, von E.: Obstetric and Gynecologic Diseases, pp. 1-176.

Krokfors: Obstetric and Gynecologic Diseases, pp. 1-176.

The cases presented were derived from the Women's Clinics and the Central Institute of Radiotherapy of the University of Helsinki and were collected during the years 1926 to 1953. The objectives of the investigation were to determine (1) the distribution by age and parity of patients with gynecological diseases treated in the hospital, and (2) the causes of the fact that certain gynecological diseases show a typical age and parity distribution of their own, and how this influence of age and parity is reflected in each particular disease. When sterilized patients and those who had been treated for complications of early pregnancies were excluded, the total number of women, para 0 to para 4, was 2,676 and of grand multiparas, 3,975. The distribution of these patients according to age and parity was compared (1) with the classification by age and parity of 54,336 women aged 17 to 100 years based on data from different parishes selected to yield as good a correspondence as possible with the above case material (second control series), and (2) with the age and parity distribution of the patients treated in the above hospitals in 1929, 1936, 1943, and 1951 (first control series).

Malignant tumors accounted for 44.5 per cent of all gynecological diseases in grand multiparas, for 19.8 per cent in the para 0 to para 4 group, and for 20.4 per cent in the first control series. The frequencies of gynecological diseases in the para 0 to para 4 group, in grand multiparas, and in the first control series varied most widely in the following conditions:

Gynecological disease	*Para 0 to para 4 (%)*	*Grand multiparas (%)*	*First control series (%)*
Myoma of the uterus	15.6	7.8	17.3
Ovarian cyst and tumor	6.0	3.3	4.7
Retroversion of the uterus	2.7	0.4	3.1
Prolapse of the uterus	4.7	15.3	5.7
Salpingo-oophoritis	28.0	5.5	23.0
Functional bleeding	7.6	13.2	10.2
Endometriosis	2.2	0.3	2.1
Carcinoma of cervix uteri	11.5	31.3	12.7
Carcinoma of corpus uteri	3.4	4.6	3.9
Carcinoma of the vulva	0.6	2.5	0.8
Carcinoma of the vagina	0.8	2.3	0.7
Sarcoma of the uterus	0.3	0.6	0.3

*These articles have been abstracted.

In summary, the influence of age and parity in selected ones of the above gynecological disorders is as follows:

Myomas of the uterus. A significant shift toward older age groups is observed in this disease as parity increases, i.e., increased parity caused myoma to occur at a more advanced age.

Prolapse of the uterus. A significant age shift appears in this disease with increased parity, i.e., numerous deliveries cause the onset to shift toward higher age groups.

Salpingo-oophoritis. An age shift in two directions is observed in this disease with increased parity. The age effect shows that the incidence of disease rises sharply from the age of 20 years to about 30 years, and decreases then more slowly, being lower in menopausal women than in the 20-year-old woman.

Functional bleeding. The age effect shows a high incidence for patients under 20; the incidence then declines with advancing age in the 20- to 30-year-old, and at the age of 35 there is a sharp increase, a maximum being reached between 45 and 50 years. There is a significant age shift due to parity, i.e., an increase in the number of deliveries causes the onset to occur in older age groups.

Carcinoma of the cervix. There is a significant age shift caused by parity, i.e., high parity shifts the onset toward older age groups. The age effect first becomes apparent at about 25 years and is initially slight; after 30 years it begins to increase fairly steeply, reaching a maximum at the age of 50. After this age the frequency decreases somewhat up to the age of 60, but then follows a drop which is steeper than the increase, through the incidence continues to be high in old age.

Carcinoma of the corpus uteri. There is a significant age shift due to parity: in nulliparas the shift occurs toward younger age groups and in grand multiparas toward older age groups. The frequency is high in nulliparous women but then it declines with an increase in parity, reaching a minimum when parity is between 4 and 5. The frequency then rises with increasing parity, so that para 10 women have the same relative incidence as nulliparas. The author concludes that carcinoma of the corpus uteri is increasing. The ratio between carcinoma of the cervix and carcinoma of the corpus has changed from 8.7:1 in 1920 and 4.5:1 (1931-1940) to 2.2:1 (1951-1957). It was suggested that excessive estrogen stimulation is a growth-promoting factor in all kinds of gynecological cancer.

Robert E. L. Nesbitt, Jr.

Vol. 39, 1960.

*Sjöstedt, S., Rooth, G., and Caligara, F.: The Oxygen Tension in the Cord Blood After Normal Delivery, p. 34.

*Lindgren, Lennart: The Cause of Fetal Head Moulding in Labor, p. 46.

*Persson, Bengt H.: Studies on the Accumulation of Certain Barbiturates in the Brain of the Human Foetus, p. 88.

Sjöstedt, Rooth, and Caligara: Oxygen Tension in Cord Blood After Normal Delivery, p. 34.

The oxygen tension was measured in the cord blood from 69 normal newborn infants after uncomplicated deliveries. The oxygen tension was measured polarographically with the Clark cell. Within the range of pO_2 observed, the errors of the analyses should be less than ±1 mm. Hg. The pH was measured with a glass electrode connected to a radiometer pH meter, type PHM 22 equipped with a galvanometer type PHA 621. The oxygen saturation was measured with a Brinkman hemoreflectometer.

The oxygen tension, pH, and oxygen saturation in the umbilical cord blood is summarized as follows:

Determinations	*Mean*	*Standard deviation*	*No.*
Arteries.			
pO_2	16.90	5.9	51
pH	7.26	0.09	51
CO_2 saturation	23.70	15.5	47
Vein.			
pO_2	28.9	6.3	68
pH	7.32	0.09	61
CO_2 saturation	60.1	13.7	57

Calculations showed that the umbilical vein on an average carries 14.1 volumes per cent O_2 and the umbilical arteries 7.8 volumes per cent. Thus, the umbilical V-A difference is 6.3 volumes per cent. The study of the oxygen tension in the umbilical cord demonstrated that the intrauterine pO_2 in the fetal systemic arteries is about 20 mm. Hg.

Robert E. L. Nesbitt, Jr.

Lindgren: Cause of Fetal Head Moulding in Labor, p. 46.

Thirty-six patients in labor have been investigated by the intrauterine tocography to find the causes of the moulding of the fetal head during the first stage of labor. Recordings were made of 1,757 contractions. The amniotic pressure, the amniotic tone, the pressures at the largest circumference of the fetal head and 3 cm. below that circumference were measured, together with the frequency of the contractions and the rate of cervical dilatation. The corresponding pressure conditions during the second stage in normal labor were also registered in 5 primigravidas and in 5 multigravidas, 208 contractions being recorded.

The investigation demonstrated that the pressure at the largest circumference of the fetal head, both during and between the contractions, is higher than the corresponding amniotic pressure and the amniotic tone as well as the corresponding pressure below the maximum circumference. This proves the conditions for the deformation of the fetal head during the first stage of labor. The greater deformation of the fetal head during the first stage of labor with hypertonic inertia is due to the higher tone at the largest circumference of the fetal head, while the diminished moulding with hypotonic inertia is accounted for by low tone at this circumference.

The corresponding pressures during the second stage of labor showed that the high pressure on the fetal head acts below the largest circumference of the fetal head. This pressure counteracts the pressure during the first stage and accounts for the diminished deformation of the fetal head during the second stage of labor.

Robert E. L. Nesbitt, Jr.

Persson: Studies on Accumulation of Certain Barbiturates in Brain of Human Foetus, p. 88.

The concentration of barbiturates in the fetus after administration of barbitone and amylobarbitone to the mother has been determined in 20 cases of therapeutic abortion in the fourth to sixth months of pregnancy. Barbitone was given by mouth in a dose of 0.5 grain twice, 16 and 3 hours, respectively, before operation and amylobarbitone as an intramuscular injection of 0.25 grain at corresponding times. Quantitative measurements of the respective barbiturates were performed on the mother's blood and urine at operation and on the umbilical cord blood and placenta, together with a homogenate of liver and different portions of the fetal brain.

The concentration of barbitone was remarkably high in the upper part of the brain stem which contained on the average twice as much barbitone per unit weight as did the cerebral cortex. Amylobarbitone appeared in the highest concentration around the fourth ventricle where also the concentration was twice that in the cerebral cortex. The blood concentrations of mother and fetus were approximately the same. Chromatographic analyses showed that barbitone occurred only as intact (nonmetabolized) substance in the tissues. With amylobarbital, both the intact substances and a probable metabolite could be demonstrated constantly in the mother's urine and in the fetal liver, in a number of cases in the mother's blood, and in certain cases in fetal blood and brain. Preliminary studies of barbiturate excretion in the urine of newborn infants, who have received the drug in utero, also show that excretion is continuously demonstrable in relatively high quantities for 3 days after the drug (amylobarbital) is given to the mother.

Abnormally high quantities of phenobarbitone are fixed in brain tissue in acidosis. This is also true for other barbiturates (barbitone). Thus, it might be expected that the fetus would be relatively more exposed to the accumulation of barbiturate in the tissues than the mother. It may be thought that the most important effect of an accumulation of pharmacologically intact barbiturate in brain tissue on the newborn infant is respiratory depression.

Robert E. L. Nesbitt, Jr.

British Medical Journal

Vol. 1, Feb. 20, 1960.

*Walker, C. W., and Pye, B. G.: The Length of the Human Umbilical Cord, p. 546.

Walker and Pye: Length of Human Umbilical Cord, p. 546.

The authors have carefully measured the lengths of umbilical cords from 223 consecutive deliveries and have subjected the mothers' charts to severe statistical analyses to see if they could find any factor which might in any way correlate with the umbilical cord length. Among the factors evaluated were the following: parity, age of mother, height of mother, weight of mother, pre-eclamptic toxemia, duration of pregnancy,

presentation, circumvolution of cord, sex, stillbirth, abnormal birth, weight of child, length of child, and duration of labor.

The only significant findings were that normal gestation and delivery can occur with any length of cord between 7 and 48 inches, that males have slightly longer cords than females, and that linear regression of cord lengths on length of pregnancy showed that there was no evidence of growth of cord length after 28 weeks. *Stuart O. Silverberg*

April 30, 1960.

*Mattingly, D., Mills, I. H., and Prunty, E. T. G.: Treatment of Simple Hirsutism, Including the Hirsute Type of Stein-Leventhal Syndrome, p. 1298.

Mattingly, Mills, and Prunty: Treatment of Simple Hirsutism, Including Stein-Leventhal Syndrome, p. 1298.

The effects of steroid therapy, consisting of prednisone 10 mg. per day combined with ethinyl estradiol, were studied in 21 cases of simple hirsutism and in 3 cases of the hirsute type of Stein-Leventhal syndrome. There was significant improvement noted in 6 patients, doubtful improvement in 9 patients, and no improvement in 9 patients. It is noted that there is no way to predict whether any patient will respond and that a problem of relapse on cessation of therapy exists so that they do not recommend routine use of the steroids in this condition in view of the occasional response.

Stuart O. Silverberg

June 4, 1960.

*Chalmers, J. A., and Fothergill, R. J.: Use of a Vacuum Extractor (Ventouse) in Obstetrics, p. 1684.

Chalmers and Fothergill: Use of a Vacuum Extractor in Obstetrics, p. 1684.

A review of the history of the vacuum principle for delivery and the present-day literature including experience with Malmstrom's vacuum extractor are presented. The instrument, its method of application, and its use are described. During the 12 months up to April, 1958, forceps were applied to 10.3 per cent of 936 deliveries. During the next 12 months the forceps rate fell to 4.1 per cent and the vacuum extractor was used in 6.6 per cent of 1,035 deliveries. In 88 cases delivery was successful with the ventouse alone. In 12 cases, forceps were used to complete the operation.

All the children weighing from 2,040 to 5,045 grams were born alive except 2 in whom intrauterine death had preceded delivery by 4 and 5 hours. There were 2 neonatal deaths, in one of which forceps delivery was undertaken for acute fetal distress in a case in which difficulty had been experienced in obtaining adhesion with the ventouse. The second was a first twin weighing 2,040 grams who died from tentorial tears 6 hours after an easy delivery. Two had small abrasions around the periphery of the caput which persisted about one week.

In 16 of the 100 cases application was made before complete dilation. The indications for interference were: long labor with dysfunction in 9, fetal distress in 6, and uterine scar in 1.

Anesthesia consisted of general anesthesia in 10 cases, pudendal block in 50, local infiltration in 36, and none in 4 cases. Episiotomy was performed in all but 8 cases.

Presentations were as follows: occipitoanterior in 57 cases, occipitotransverse in 26, and occipitoposterior in 17. Babies in the posterior occiput positions were delivered as persistent posterior in 10 cases and spontaneously rotated in 7 cases. Twenty-four of the 27 cases of transverse occiput spontaneously rotated, 1 delivered persistent transverse, and 1 required Kielland forceps rotation. Of 2 with brow presentations, 1 was a second twin and was delivered as a brow presentation in a large pelvis. The second brow was flexed automatically by means of a posterior cephalic application of the instrument and the infant was delivered as an occipitoposterior, with autorotation through 140 degrees having occurred. In 3 cases of frank breech presentations with delay in the second stage, the ventouse was applied to the anterior buttock with resultant descent from high to low pelvis so that an easy extraction could be carried out.

The authors conclude that the vacuum extractor is a valuable addition to the obstetrician's armamentarium and it can replace the forceps in a wide range of conditions. It can be used with safety to both mother and child and, in addition, may be used during the first stage of labor to augment pains and promote dilatation of the cervix so that early delivery becomes possible.

Rotation of the occipitoposterior or transversely arrested head can in most instances be more easily and more physiologically effected with the ventouse than either manually or with forceps. *Stuart O. Silverberg*

Item

New gynecological society formed in New York City

A new society known as the New York Gynecological Society has been formed in New York City. The Society was incorporated under the laws of the State of New York by a committee of physicians, Carl Javert, M.D., Joshua Davies, M.D., and Alexander Brunschwig, M.D., who also are the directors.

The purpose of the Society is to promote research and to create a forum for the discussion of problems and advances in the field of gynecology and obstetrics. The membership is composed of specialists certified in gynecology and obstetrics and other specialists interested and active in these subjects.

For further information write to: M. Leo Bobrow, M.D., Secretary, New York Gynecological Society, 590 West End Avenue, New York City.

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Volume 80
July-December, 1960
The C. V. Mosby Company
St. Louis
1960

American Journal of Obstetrics and Gynecology

in addition to those listed on the front cover,

the Journal is the official publication

of the following societies:

NEW YORK OBSTETRICAL SOCIETY
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Volume 80
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Printed in the United States of America

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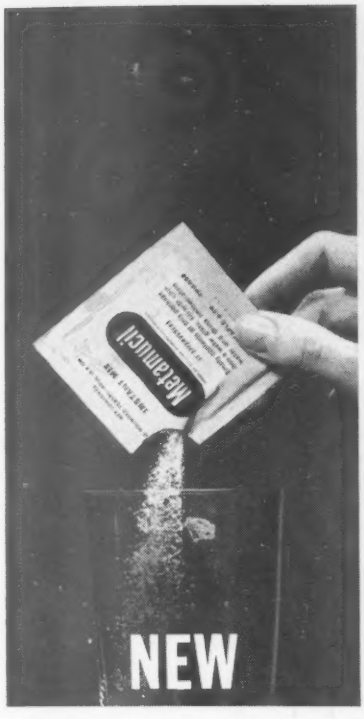

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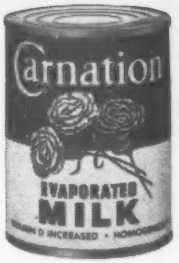

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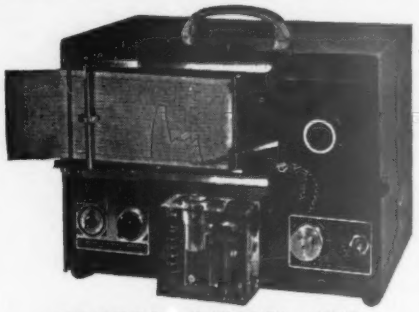

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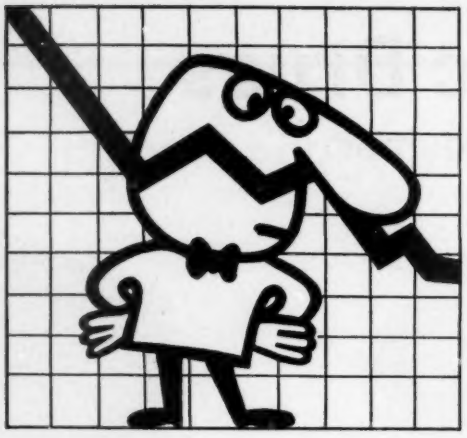

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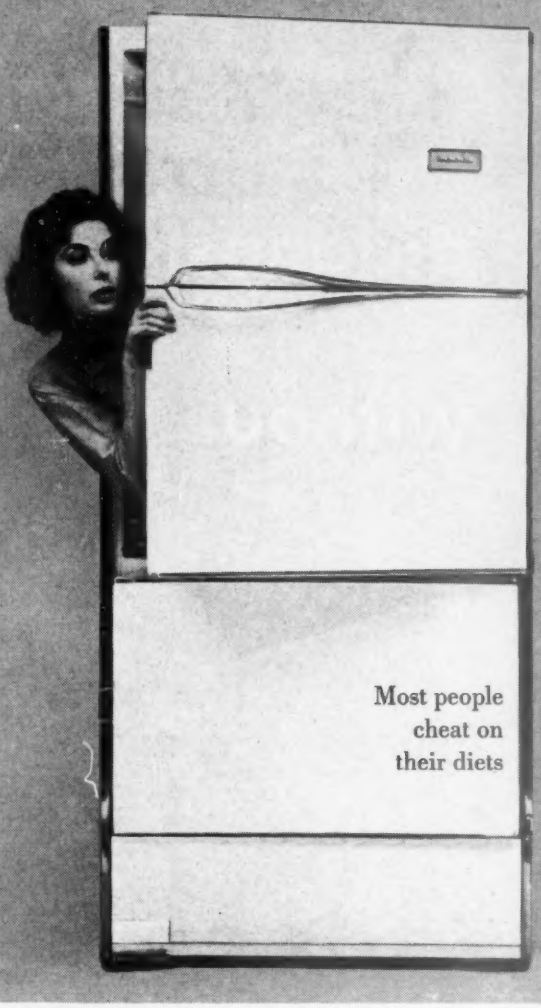

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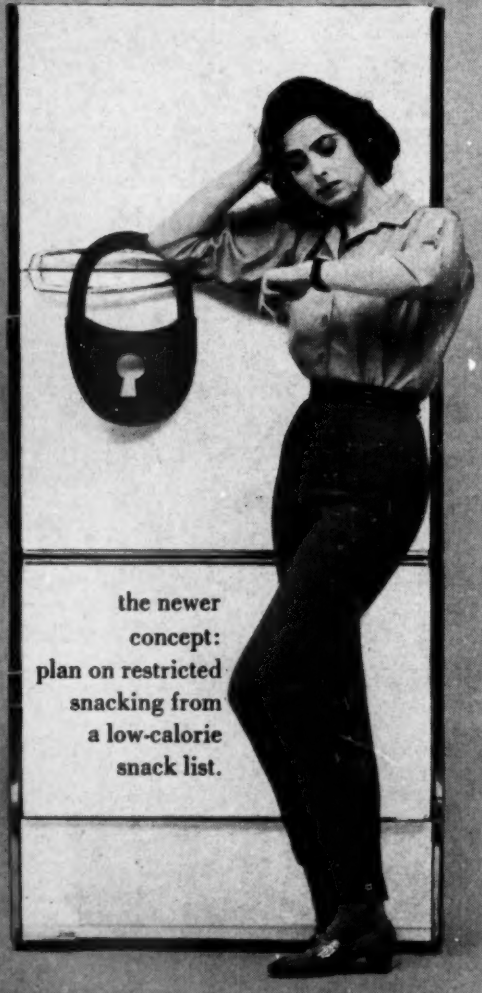

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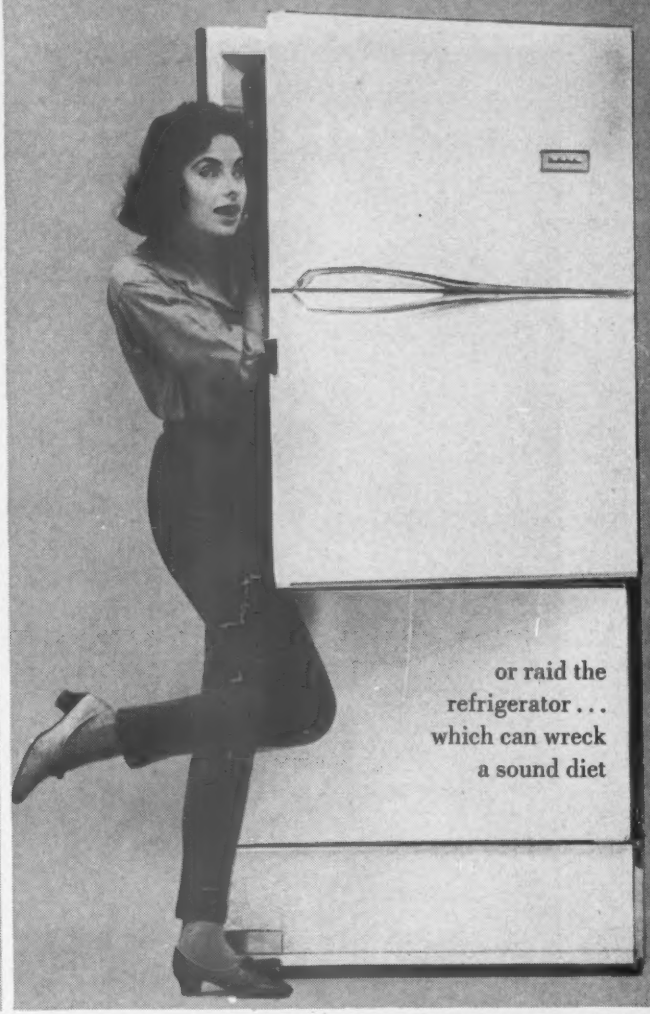

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Few foods known to man provide a higher ratio of nutrient value to calories than do eggs.

The quality of egg protein is a standard against which the proteins of other foods are measured.

The cholesterol and fatty acid contents of two eggs—traditionally a widely preferred breakfast—fit well into the daily diet, even when lessened fat intake is recommended.

Because of their high nutrient value, their easy digestibility, compatibility, and nutritional complementation of other foods, eggs are included in the recommended dietary* for many conditions in which diet adjustment is indicated.

Eggs are listed in the daily recommendations of nourishing liquid, restricted fiber, low sodium, restricted purine, low-calorie, and many other diets.

**Recommended in the diet manuals of teaching institutions.*

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

Poultry and Egg National Board
8 South Michigan Avenue, Chicago 3, Illinois

the gentlest doctors in town

stop pain with Nupercainal®

(dibucaine CIBA)

...For minor cuts and burns, sunburn, hemorrhoids, removing sutures, performing routine office surgery, making instrument examinations. And, to best suit every situation, there's a choice of Ointment, Cream, Lotion, Suppositories.

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CIBA
SUMMIT, N. J.

Complete information available on request.

stop hemorrhoid pain with
NUPERCAINAL SUPPOSITORIES
exact dosage • fast acting

2/2817NB

now—two FILIBON formulas

for individualized pre- and postnatal support

***two formulations*—both phosphorus-free, both with noninhibitory intrinsic factor and well-tolerated iron—providing greater flexibility in meeting individual requirements in pregnancy and lactation.**

you can recommend: FILIBON® Capsules

Prenatal Supplement Lederle

Each capsule contains:

Vitamin A (acetate)	4,000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Mononitrate (B_1)	3 mg.
Pyridoxine (B_6)	1 mg.
Niacinamide	10 mg.
Riboflavin (B_2)	2 mg.
Vitamin B_{12} with AUTRINC® Intrinsic Factor Concentrate	⅙ N.F. Oral Unit
Ascorbic Acid (C) (as Calcium Ascorbate)	50 mg.
Vitamin K (Menadione)	0.5 mg.
Ferrous Fumarate (Elemental iron, 30 mg.)	91.2 mg.
Fluorine (as CaF_2)	0.015 mg.
Copper (as CuO)	0.15 mg.
Iodine (as KI)	0.01 mg.
Potassium (as K_2SO_4)	0.835 mg.
Manganese (as MnO_2)	0.05 mg.
Magnesium (as MgO)	0.15 mg.
Molybdenum (as $Na_2MoO_4.2H_2O$)	0.025 mg.
Zinc (as ZnO)	0.085 mg.
Calcium Carbonate	575 mg.

or you can prescribe: FILIBON® F.A. Capsules

Prenatal Supplement with Folic Acid Lederle

The complete FILIBON formula, *plus* 1 mg. of Folic Acid, essential for the prevention of the common megaloblastic anemias of pregnancy.

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A Division of
AMERICAN CYANAMID COMPANY
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NEEDED: THE APPETITE SUPPRESSANT STRONG ENOUGH AND SAFE ENOUGH TO DO THE JOB

Ambar controls many cases of overeating/obesity refractory to usual therapy. To strengthen the will for successful dieting, the methamphetamine-phenobarbital in Ambar is designed to improve mood without harmful CNS overstimulation. Available in different forms to enable individualization of dosage: **AMBAR #1 EXTENTABS,** 10-12 hour extended action tablets, methamphetamine HCl 10.0 mg., phenobarbital 64.8 mg. **AMBAR #2 EXTENTABS,** methamphetamine HCl 15.0 mg., phenobarbital 64.8 mg. Also conventional **AMBAR TABLETS,** methamphetamine 3.33 mg., phenobarbital 21.6 mg.

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Ambar™ #1 Extentabs® / Ambar™ #2 Extentabs®

CONSISTENTLY GOOD CLINICAL RESULTS IN TRICHOMONAL AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder) cured 143 of 161 patients with vaginitis due to Trichomonas vaginalis, Candida (Monilia) albicans, or both. "Almost immediate symptomatic improvement was noted with the first insufflation."

Criteria for cure: freedom from infecting organisms as well as symptoms on repeated examinations during a three-month follow-up. This cure rate of 88.8% is "surprisingly similar" to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.: J.M.A. Georgia 48:167, 1959.

TRICOFURON®

IMPROVED

2-step treatment brings swift relief, eradicates stubborn trichomonads, Candida (Monilia) albicans, Hemophilus vaginalis

1. POWDER for weekly insufflation in your office. MICOFUR®, brand of nifuroxime, 0.5% and FUROXONE®, brand of furazolidone, 0.1% in an acidic water-dispersible base.

2. SUPPOSITORIES for continued home use —1st week one suppository in the morning and one on retiring. After 1st week, one suppository at night may suffice.

Continue use of suppositories during menses. Treatment should be continued throughout a complete menstrual cycle and for several days thereafter. MICOFUR 0.375% and FUROXONE 0.25% in a water-miscible base.

Rx new box of 24 suppositories with applicator for more practical and economical therapy.
Also available:
box of 12 suppositories with applicator.

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STOP ITCHING HELP SKIN RESIST IRRITATION

LIDA-MANTLE™

- *Relieves itching and topical pain within minutes . . ."superior to any existing local anesthetic."*[1]
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- *The exclusive* ACID MANTLE *vehicle soothes sensitive skin, speeds healing and wards off recurrences by rebuilding the protective barrier of acidity that helps skin resist inflammation, irritation and infection.*

Available as Creme in ½ oz. and 1 oz. tubes.
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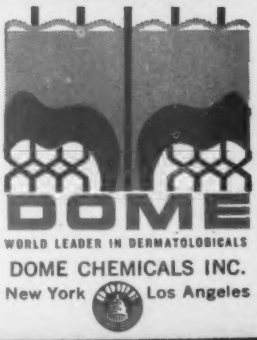
*Reg. T.M. Astra Pharmaceutical Products, Inc. U.S. Pat. No. 2,441,498. †Reg. T.M. Dome Chemicals Inc.
1. Crawford, O. B.: Anesthesiology 14:278, 1953. 2. Wiedling, S.: Xylocaine, The Pharmacological Basis For its Clinical Use, Stockholm, Almquist and Wiknell, 1959.



WORLD LEADER IN DERMATOLOGICALS
DOME CHEMICALS INC.
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Each tablet contains:
Provera (medroxyprogesterone acetate) 2.5 mg.
Cardrase (ethoxzolamide) ..... 35 mg.
Levanil (ectylurea) ..... 300 mg.

DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days before the period.

THE UPJOHN COMPANY / KALAMAZOO, MICHIGAN

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GETS AT THE PROBABLE CA

to restore hormonal balance...

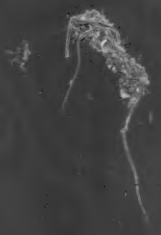
corrective therapy Because Cytran contains the new progestin, Provera,† you can now reach the probable *cause* of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.

to comfort the patient...

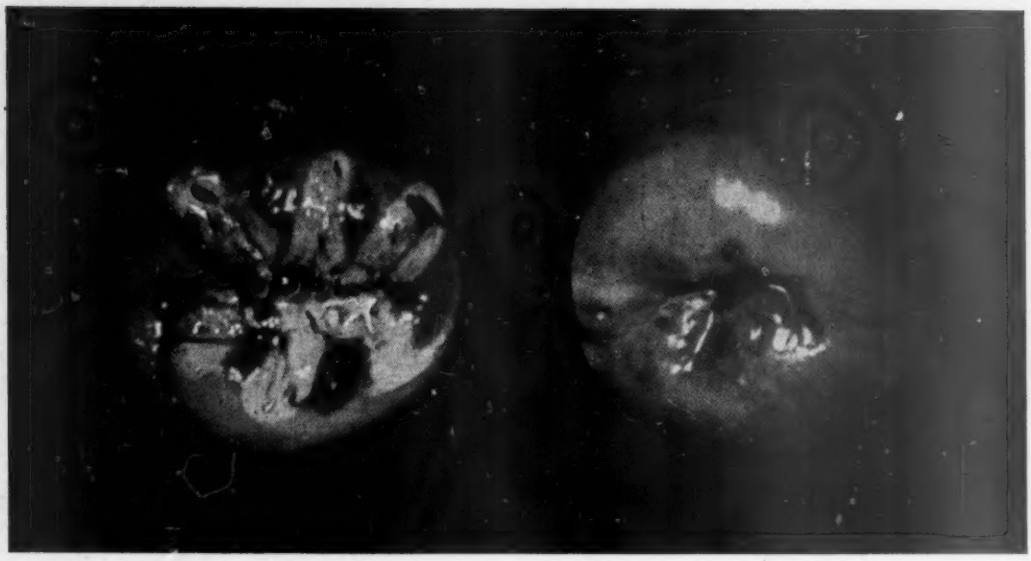
symptomatic therapy An effective diuretic (Cardrase†) and a mild tranquilizer (Levanil†) afford symptomatic relief while Provera works to effect a restoration of hormonal balance. They also supplement the activity of Provera in those rare cases where restoration of hormone balance does not completely eliminate edema and anxiety/tension.

*TRADEMARK †TRADEMARK, REG. U.S. PAT. OFF.

Upjohn



CAUSE OF PREMENSTRUAL TENSION



For your OB-GYN patients: fight infection, facilitate healing

Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, FURACIN *helps to provide a shorter, more comfortable convalescence. Infection is promptly controlled; discharge, irritation and malodor reduced; healing hastened.* FURACIN *is highly active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.*

FURACIN®

brand of nitrofurazone

Vaginal Suppositories

FURACIN 0.3% in a water-miscible base which melts at body temperature. Box of 12, each 2 Gm. suppository hermetically sealed in yellow foil.

Cream

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator.

THE NITROFURANS—
a *unique* class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

The Pregnant

– and a natural way to meet her special need for calcium
– with low-calorie Carnation Instant

Drinking enough milk during pregnancy to assure sufficient calcium has posed the problem of unwanted fat calories – till recently.

Now a *natural* way to help assure your patients' good calcium and nutritional status is the excellent new food – *new Carnation Instant Nonfat Dry Milk mixed 25% overstrength.*

One-third cup extra crystals per liquid quart when mixing provides 25% more calcium, protein, and B-vitamins than ordinary nonfat milk. Because your patients can add this additional amount of Carnation Instant Nonfat, they get *needed* nutrition – *without* excessive calories. It's richer, more delicious flavor is a *natural* way to *extra* nutrition they will enjoy. Costs them only 12¢ a quart.

ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA

After a history and a physical ruled out organic disease, the physician diagnosed the case as recurring states of anxiety. To relieve these symptoms for this busy, on-the-go housewife, he prescribes Meprospan-400, the *only* meprobamate in *sustained-release* form.

As directed, the patient takes one Meprospan-400 capsule at breakfast. Her symptoms of tension and nervousness are soon relieved, and she will not have to remember to take another capsule until dinnertime.

Calm and relaxed, the patient is no longer upset by the pressures and irritations met in everyday life, nor is she likely to be incapacitated by autonomic disturbances, drowsiness, ataxia or other untoward reactions.

Alert and attentive, the patient participates in a P.T.A. meeting, following her second capsule of Meprospan-400 taken with the evening meal. Meprospan-400 does not decrease her mental efficiency or interfere with her normal activities or behavior.

Peacefully asleep, the patient enjoys beneficial rest . . . Meprospan-400 has relieved the tensions that previously prevented sleep or kept her tossing and turning throughout the night.

most widely prescribed tranquilizer . . .
most convenient dosage form . . .

ONE CAPSULE LASTS 12 HOURS

Meprospan®-400

400 mg. MILTOWN® SUSTAINED-RELEASE CAPSULES

Usual dosage: One capsule at breakfast lasts all day, one capsule with evening meal lasts all night. **Supplied:** Meprospan-400, each blue-topped *sustained-release* capsule contains 400 mg. Miltown. **Also available:** Meprospan-200, each yellow-topped *sustained-release* capsule contains 200 mg. Miltown. **For children:** Capsules can be opened and the coated granules mixed with soft foods or liquids.

Both potencies in bottles of 30.

Samples and literature available on request.

WALLACE LABORATORIES / *Cranbury, N. J.*

Capillary protective measures in pregnancy

Prenatal treatment and threatened abortion

During pregnancy, fragile capillaries, increased capillary permeability, decidual bleeding, and the tendency toward edema are well recognized. Essential capillary protective factors are an integral part of the prenatal regimen.

The inclusion of Hesperidin or other citrus bioflavonoids as a "precautionary measure" in every pregnancy and as an "essential measure" in habitual aborters insures the restoration and maintenance of capillary integrity and helps prevent spontaneous abortion.

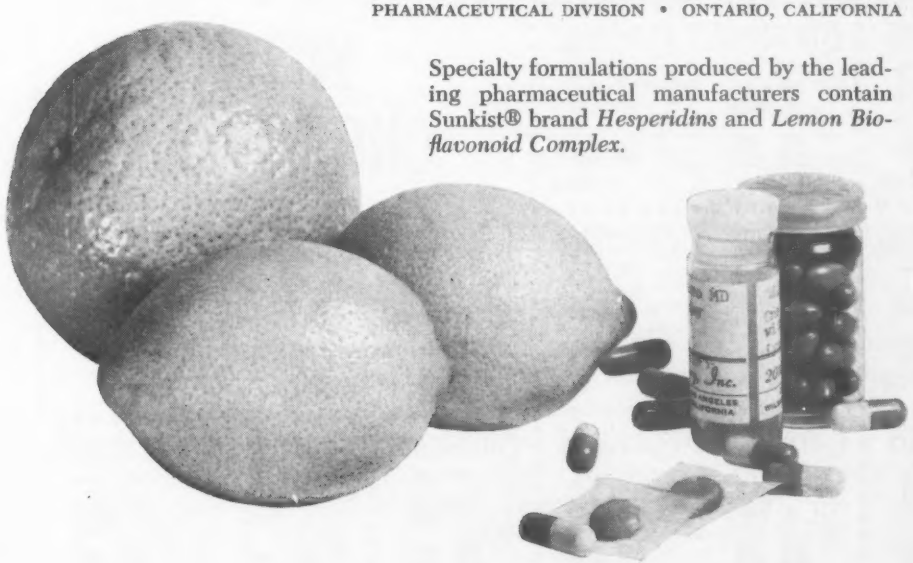
The rationale of Hespiridin and other citrus bioflavonoids – in conjunction with vitamin C, nutritional factors and other therapeutic measures – as adjuncts, is based on the premise that capillary involvement may be a contributing factor in spontaneous abortion and erythroblastosis fetalis.

Hesperidin, Lemon Bioflavonoid Complex and their naturally occurring synergist ascorbic acid are readily available capillary protective factors for the restoration and maintenance of capillary integrity and function.

Sunkist Growers

PHARMACEUTICAL DIVISION • ONTARIO, CALIFORNIA

Specialty formulations produced by the leading pharmaceutical manufacturers contain Sunkist® brand *Hesperidins* and *Lemon Bioflavonoid Complex.*



Greetings
Christmas
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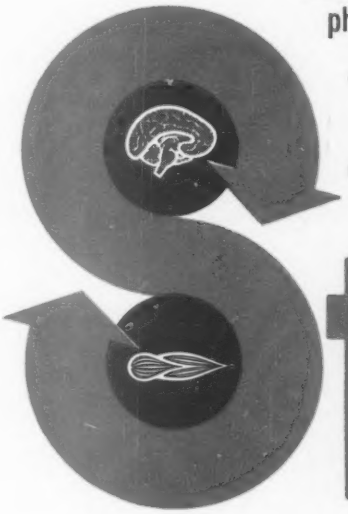
WITH
CHRISTMAS
SEALS
ANSWER YOUR CHRISTMAS
SEAL LETTER TODAY

a new, improved, more potent relaxant for anxiety and tension

- effective in half the dosage required with meprobamate
- much less drowsiness than with meprobamate, phenothiazines, or the psychosedatives
- does not impair intellect, skilled performance, or normal behavior
- neither depression nor significant toxicity has been reported



alert tranquillity

Striatran®

EMYLCAMATE

- a familiar spectrum of antianxiety and muscle-relaxant activity
- no new or unusual effects—such as ataxia or excessive weight gain
- may be used in full therapeutic dosage even in geriatric or debilitated patients
- no cumulative effect
- simple, uncomplicated dosage, providing a wide margin of safety for office use

STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

Adult Dosage: One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

Supply: 200 mg. tablets, coated pink, bottles of 100.

While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

STRIATRAN IS A TRADEMARK OF MERCK & CO., INC.

26 ~~25~~ Years Successful Use Without a Diaphragm

SINCE 1934

WHITTAKER LABORATORIES, Inc.

PEEKSKILL, NEW YORK.

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ATLANTIC TO PACIFIC

and

PANAMA TO ARCTIC

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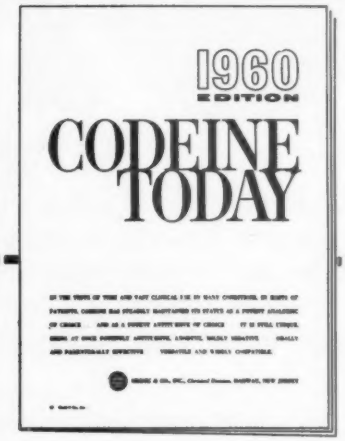
NEW FACTS ABOUT CONTROLLING PAIN AND COUGH

New Comprehensive Supplement to 'Codeine Today' Highlights Newest Data on One of Medicine's Most Useful but Underestimated Drugs



Just 20 minutes reading will review for you essential clinical findings on the use of Codeine. New supplement presents concise quotes by today's authorities on the use of codeine in conditions from the common cold to sickle cell disease. Tells when to use, how to use and where to use this versatile drug. Supplement is attached to 'Codeine Today' which reviews 1957-1958 data. This information is of interest to practically every practitioner. Bibliography now totals more than 80 references.

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MERCK & CO., INC., Medicinal Products Department
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Please send me_____copies of Codeine Today with new 7-page supplement.

PHYSICIAN'S NAME AND ADDRESS

PERFORMANCE PRE-MEASURED

Precision lenses must meet a high standard of excellence if they are to perform with the predictability, accuracy and reliability which the scientist requires.

An equally exacting standard of excellence is required of the thyroid preparation used by the physician treating hypothyroidism. For consistent clinical performance, from dose to dose, he can use only the most carefully processed and critically controlled preparation. Proloid meets this need by providing uniform metabolic potency and a safe, predictable clinical response from tablet to tablet. The reason—Proloid's exclusive biological assay—performance pre-measured. Yet, Proloid costs only a few pennies more a month over ordinary thyroid. GP04

dependable
safe
economical

THYROID PROLOID®

WARNER CHILCOTT

MORRIS PLAINS, N.J.

when reassurance
is not enough...

Ritalin®

helps brighten the day

Clinicians report how RITALIN gives dispirited patients a lift...with safety

"These patients represented the types of cases which might come into any doctor's office for treatment ...the chronically ill and incurables, the convalescing group, the 'low' patients, depressed because of pressure of present-day living, and the group who were on medications which caused depressed states."

"The effect [of Ritalin] lasted about four hours, gave the patient a feeling of well-being and that life was worth living. Their worries seemed to disappear; they were alert, fatigue disappeared, and they could go all day without tiring. The effects gradually disappeared with no extreme let-down or rebound effect."

"... the drug [Ritalin] had no effect on blood pressure, the blood count, urine or blood sugar, did not depress the appetite, and produced no tachycardia. There was no evidence of any allergic manifestations in any of the cases."

—Natenshon, A. L.: Dis. Nerv. System *17*:392 (Dec.) 1956.

"A double blind study of the mood elevating properties of Ritalin® in 112 patients showed statistically significant effect.... This drug offers great help in patients in whom elevation of the mood is desirable."

—Landman, M. E., Preisig, R., and Perlman, M.: J. M. Soc. New Jersey *55*:55 (Feb.) 1958.

"It [Ritalin] causes mild depressions to vanish.... It changes dull, apathetic patients into more alert, interested ones."

"It stimulates apathetic and negativistic patients to more normal, productive activity."

—Pennington, V. M.: Mississippi Doctor *35*:57 (Aug.) 1957.

Complete information available on request.

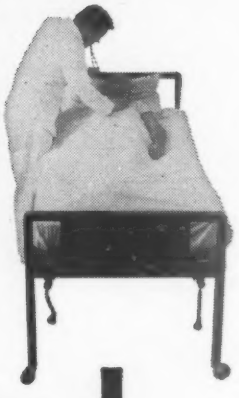
SUPPLIED: TABLETS, 5 mg. (yellow), 10 mg. (light blue), 20 mg. (peach colored)

RITALIN® hydrochloride
(methylphenidate
hydrochloride CIBA)

CIBA
SUMMIT, NEW JERSEY

2/2776MK

in cardiac edema of varying severity



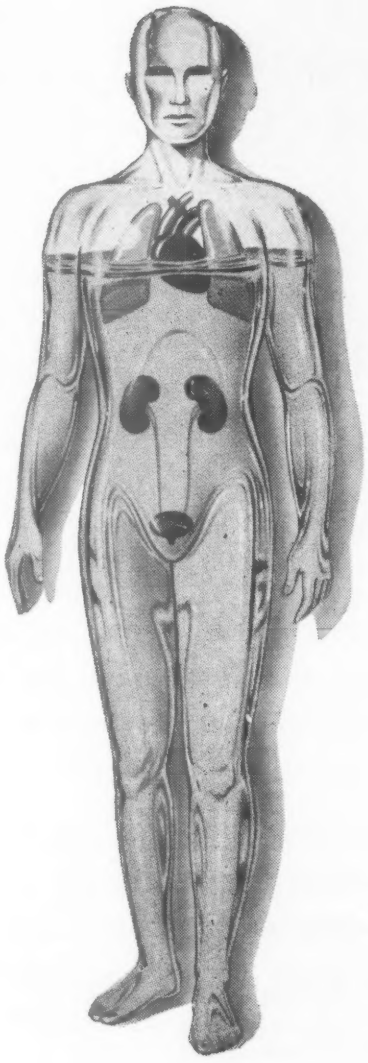
weight loss ranged from 4 to 45 lbs. on

HYDRODIURIL®

HYDROCHLOROTHIAZIDE

increased potency—without corresponding increase in side effects

Sackner, M. A., Wallack, A. A. and Bellet, S.: Am. J. M. Sc. 237:575, (May) 1959.



"The severity of the congestive heart failure . . . was as follows: Class IV (9 patients), Class III (5 patients), and Class II (1 patient).". . ."Weight loss ranged from 4 to 45 pounds over a period of 3 to 17 days with an average of 2.4 pounds a day."

DOSAGE: One or two 50 mg. tablets of HYDRODIURIL once or twice a day.

SUPPLIED: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., INC.

Additional information on HYDRODIURIL is available to the physician on request.

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Division of Merck & Co., INC. Philadelphia 1, Pa.

in 'normal' backache of pregnancy

fast pain relief

potent muscle relaxation

safe for prolonged use

SOMA provides both muscle relaxant and analgesic actions... relaxes the stiffness of skeletal muscle which causes the pain of the backaches so often experienced in the later months of pregnancy.

easy to use—usual adult dose is one 350 mg. tablet three times daily and at bedtime

SUPPLIED: as 350 mg. white tablets, bottles of 50; also available for pediatric use, 250 mg. orange capsules, bottles of 50

Literature and samples on request

SOMA® (carisoprodol Wallace)

WALLACE LABORATORIES, Cranbury, N. J.

CONSISTENT RESPONSE IN VAGINAL INFECTIONS

antibacterial, antimonilial, antitrichomonal effects—optimal dispersion, prolonged retention

85% success:[1,2] Triburon Chloride—the clinically proven microbicide—provides rapid symptomatic relief as well as control of trichomonal, monilial and non-specific vaginitis. In one study,[1] discharge, itching and burning disappeared in 67 of 73 women after only 3 or 4 applications; after two weeks, cultures were negative in 61 patients. Similar results were noted in another series of 55 women.[2]

now available in two forms

New TRIB VAGINAL SUPPOSITORIES provide the efficacy of Triburon Chloride in a water-soluble, self-emulsifying base that enhances dispersion and prolongs therapeutic effects, even in the presence of profuse discharge. TRIB VAGINAL SUPPOSITORIES are provided with reusable plastic applicators.

Proven TRIBURON VAGINAL CREAM—white, nonstaining, virtually non-irritating to the vaginal mucosa, with no hint of medicinal odor. Disposable applicators are supplied with the cream.

Indications: TRIB VAGINAL SUPPOSITORIES and TRIBURON VAGINAL CREAM for vulvitis and vaginitis due to Trichomonas vaginalis, Candida albicans, Hemophilus vaginalis as well as mixed infections; after cauterization, conization and irradiation; for surgical and postpartum treatment. Therapy may be continued during pregnancy and menstruation.

Supplied: TRIB VAGINAL SUPPOSITORIES—Boxes of 24, with reusable applicator. TRIBURON VAGINAL CREAM—3-ounce tubes with 18 disposable applicators. Consult literature for dosage requirements, available on request, before prescribing.

ROCHE LABORATORIES
Division of Hoffmann-LaRoche Inc.

References: 1. N. Mulla and J. J. McDonough, Ann. New York Acad. Sc., 82: (Art. 1), 182, 1959. 2. L. E. Savel, D. B. Gershenfeld, J. Finkel and P. Drucker, ibid., p. 186.

NEW

Trib

T.M.

contains Triburon Chloride 0.1%

Vaginal Cream & Suppositories

FORMERLY TRIBURON VAGINAL CREAM
decisive microbicidal therapy in a delicate matter
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IN BRIEF

Vistaril®
HYDROXYZINE HYDROCHLORIDE
Parenteral Solution

Vistaril is a rapid-acting calmative with a wide margin of safety. Its prepartum use generally permits a reduction in dosage of narcotics and barbiturates. Vistaril's antiemetic properties further enhance its pre- and postpartum usefulness.

ACTIONS & INDICATIONS: Vistaril, as part of a prepartum regimen, can safely relax your patients by allaying fear and apprehension.

ADVANTAGES: Vistaril produces a calming effect without hypnosis. Vistaril provides direct and secondary muscle relaxation. Vistaril apparently is nonaddicting — discontinuance after months of treatment has not produced withdrawal symptoms. Vistaril has a remarkable record of safety, when used in recommended dosage. Unlike the phenothiazines, parkinsonism and blood or liver toxicities have not been reported with Vistaril. Unlike the rauwolfia derivatives, Vistaril acts rapidly, does not increase gastric secretions, and there have been no reports of nasal congestion, drug-induced depression, or sinusitis associated with its use. Unlike the meprobamates, there have been no reports of incoordination, ataxia, abdominal discomfort, anorexia, nausea, vomiting, diarrhea, allergic dermatitis, or anaphylactic reactions. VISTARIL PARENTERAL SOLUTION permits rapid action and may be given via I.M. or I.V. routes.

CONTRAINDICATIONS: There are no known contraindications to Vistaril.

SIDE EFFECTS AND PRECAUTIONS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing upon reduction of dosage or within a few days of continued therapy. Dryness of mouth may be encountered at higher dosages. The potentiating action of hydroxyzine must be taken into consideration when it is used in conjunction with C.N.S. depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is for 24-48 hours, unless changed by judgment of physician.

ADMINISTRATION AND DOSAGE: Vistaril dosage varies with the state and response of each patient, rather than on a weight basis. Dosage should be individualized by the physician for optimum results. The usual parenteral dosage in prepartum sedation is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n., (alone or in conjunction with reduced dosages of narcotics).

HOW SUPPLIED: *Vistaril Parenteral Solution*—10 cc. vials and 2 cc. Steraject® Cartridges, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. *Vistaril Capsules* (as the pamoate)—25, 50, and 100 mg. *Oral Suspension* (as the pamoate)—25 mg. per 5 cc. teaspoonful.

More detailed professional information available on request.

PFIZER LABORATORIES
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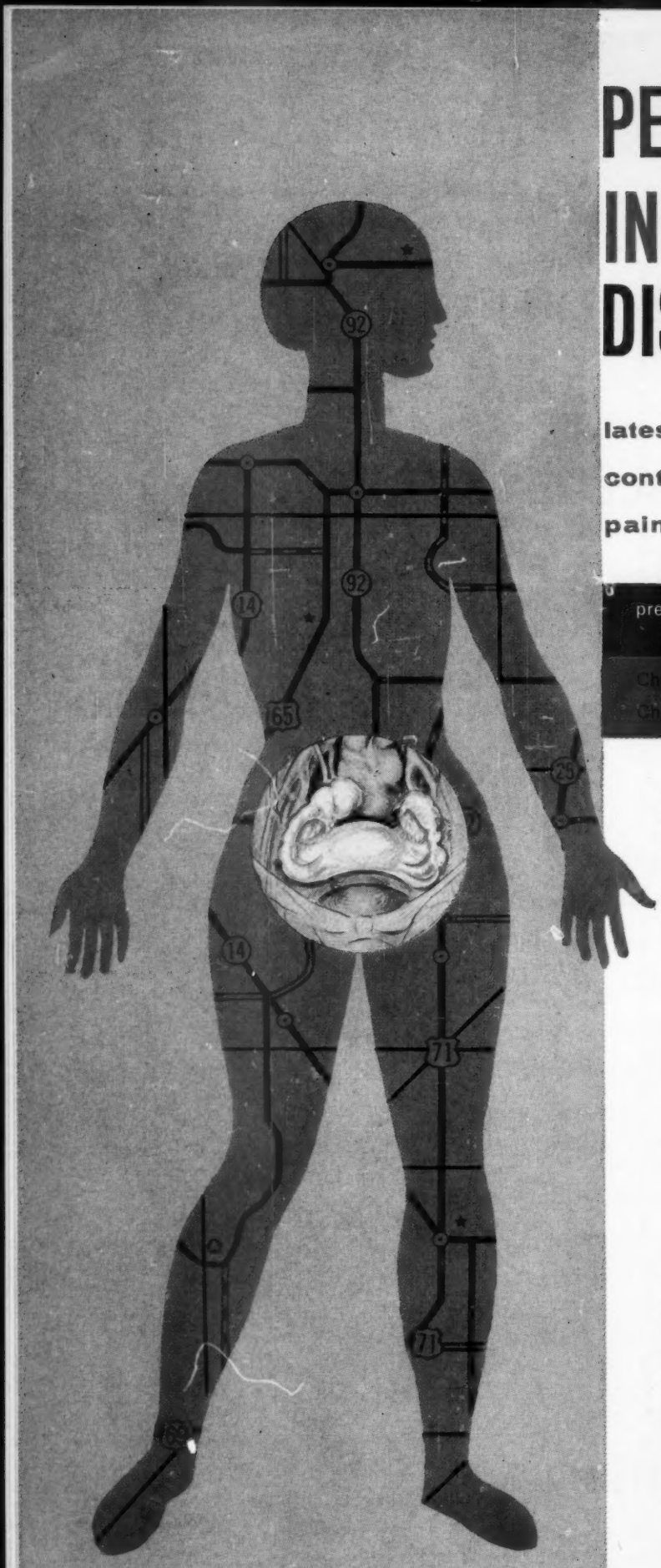

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1. Reich, W. J., and Nechtow, M. J.: Am. Pract. & Digest Treat. *11*:45, 1960. 2. Reich, W. J., and Nechtow, M. J.: Scientific Exhibit, Chicago Med. Soc. (March) 1960.

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Bibliography: 1. Finegold, Wilfred J.: Internat. J. of Fertil. 3:143 1958
2. Palmer, A.: Internat. J. of Fertil. 4:365 1959

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Seventeen patients[1] with presumed endometriosis selected for pseudopregnancy treatment were given Enovid on a "schedule of 10 mg. daily for ten days, 20 mg. daily for two weeks, and 30 mg. daily thereafter." Treatment was continued for fourteen to twenty weeks.

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1. Andrews, M. C.; Andrews, W. C., and Strauss, A. F.: Effects of Progestin-Induced Pseudopregnancy on Endometriosis: Clinical and Microscopic Studies, Am. J. Obst. & Gynec. 78:776 (Oct.) 1959.
2. Kistner, R. W.: Endometriosis and Infertility, Clin. Obst. & Gynec. 2:877 (Sept.) 1959.

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References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

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References:

1. Bennett, E. T., and McCann, E. C.: J. Maine M. A. *45*:225. 2. Eichner, E., *et al.*: Obst. & Gynec. *6*:511. 3. Nulsen, R. O., *et al.*: Am. J. Obst. & Gynec. *65*:1048.

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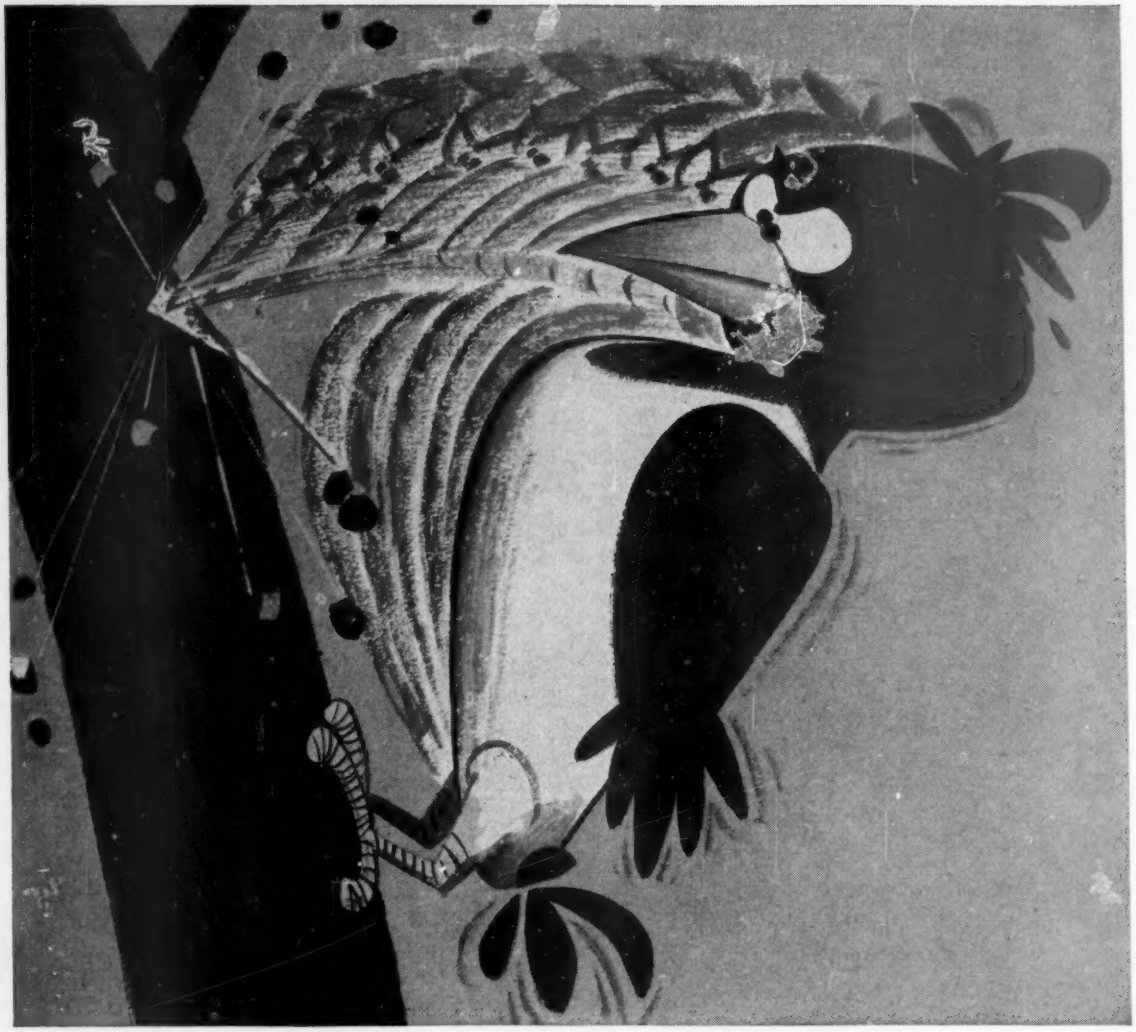

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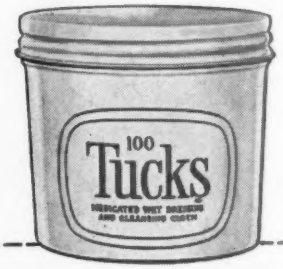

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and bacteriologic **CURES**"
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was obtained in 100%, and
bacteriologic **CURES** in 82.5%"[3]
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in mixed infections "complete
symptomatic and bacteriologic
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clinically and bacteriologically
(as indicated by vaginal
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References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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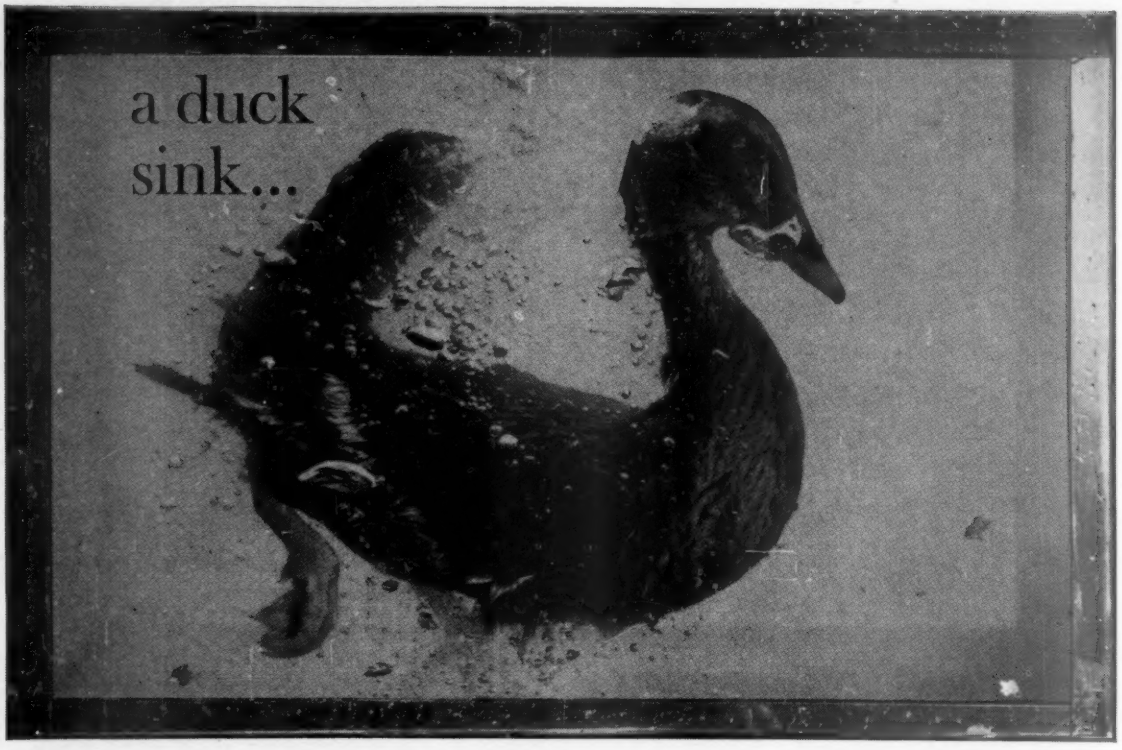

produces soft, normal stools in functional constipation

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CONTROL PRENATAL WEIGHT GAIN AND PROVIDE FULL NUTRITIONAL SUPPORT...
with no undesirable CNS stimulation and no pressor effects

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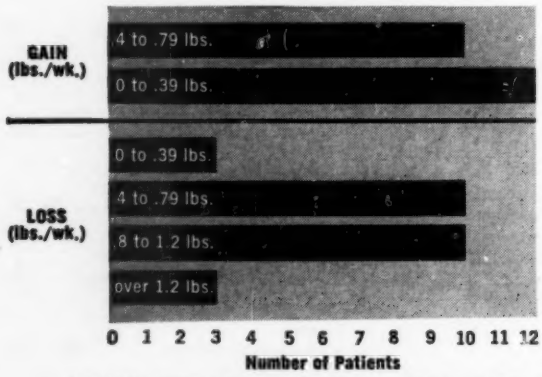

Note: The average length of therapy was 8.6 weeks. Two patients had no weight change. Adapted from Jordan[2]

Safe...for the mother and fetus: "Diethylpropion does not produce central nervous system stimulation, insomnia, or any significant change in the blood pressure or pulse rate...No abnormalities of the rate or rhythm of the fetal heart were noted during the study [50 patients treated]."[2] In another study on 138 gravida, Nulsen reports, "there have been no abnormalities noted among the babies and, therefore, it is apparent that the use of diethylpropion during pregnancy is not harmful to the fetus."[3]

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DOSAGE: One tablet t.i.d. taken one hour before meals. If desired, a fourth tablet may be taken mid-evening.

SUPPLY: Bottles of 100 orange, coated tablets. B only.

REFERENCES: 1. Nulsen, R. O.: *Curr. Therapeut. Res.* 2:102 (March) 1960. 2. Jordan, M. J.: "Safe and Effective Weight Control in Pregnancy," to be published. 3. Nulsen, R. O.: Personal communication. 4. Alfaro, R. D.; Gracanin, V., and Schlueter, E. A.: *Journal-Lancet*, in press. 5. Spielman, A. D.: *Mich. Acad. Gen. Pract. Symposium*, Detroit, 1959.

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